2016

PREDICTORS OF CAFFEINE-RELATED WITHDRAWAL SYMPTOMS IN COLLEGE FRESHMEN

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A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science at Virginia Commonwealth University

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July 21, 2016

Acknowledgements

This project would not have been possible without the continual support, guidance, and enthusiasm of my mentor and advisor, Dr. Dace Svikis. Dr. Svikis' influence in my professional development and research has been extraordinary, and I have been privileged to complete this project under her direction and expertise. I would also like to extend appreciation to my committee members, Dr. Rosalie Corona and Dr. Pamela Dillion, for their valuable contributions and support. Lastly, I thank my wife, Brianna, for her unconditional support, love, patience, and encouragement.

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Abstract

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While caffeine withdrawal has been well-characterized, research on caffeine intake and factors associated with withdrawal has been limited. The present study examined prevalence rates of caffeine use and identified psychosocial factors associated with having caffeine withdrawal headaches (CWH). Participants were N = 1,989 college freshmen who participated in the 2011 Spit for Science project. Caffeine use was reported by 80% of the sample. Females were more likely than males to consume caffeine, and soda was the primary source of caffeine for both genders. As hypothesized, daily caffeine users were more likely to report CWH than non-daily users. When multivariable analyses examined other variables identified through univariable analyses, the most parsimonious model for distinguishing between those with and without CWH included the following set of predictor variables: daily caffeine use; female; non-white minority; peers with alcohol problems; greater neuroticism, and those reporting maternal depression or anxiety.

Predictors of Caffeine-Related Withdrawal Symptoms in College Freshmen

Introduction

The markedly different means of caffeine self-administration, in addition to the widely different social and cultural contexts in which caffeine is consumed, has branded caffeine as the most widely used psychoactive drugs in the world (Benowitz, 1990; Gilbert, 1984; Griffiths & Chausmer, 2000; Griffiths & Mumford, 1996, 2000; Juliano, Ferré & Griffiths, 2014; Smith, 2005; Winston, Hardwick, & Jaberi, 2005). While population-level data on caffeine intake throughout the world and the United States has been examined (Frary, Johnson, & Wang, 2005; Fulgoni, Keast, and Lieberman, 2015; Mitchell, Knight, Hockenberry, Teplansky, & Hartman, 2014), accurate estimates of caffeine consumption has proven challenging since caffeine intake varies across different population groups and caffeine content varies considerably across different beverage types (coffee, tea, energy drinks).

Most caffeine users consume it without experiencing adverse consequences. However, like many psychoactive substances, regular (daily) use of caffeine can lead to a variety of physical and psychosocial problems (e.g., heart disease, sleep disturbance). Furthermore, caffeine use can lead to physical dependence and abrupt cessation of such use can produce symptoms of withdrawal. Empirical research has supported the addition of Caffeine Withdrawal to the DSM-5 (APA, 2013), and headaches are considered the hallmark symptom of this disorder among regular caffeine users (Juliano et al., 2014). Apart from caffeine consumption itself, however, little is known about other variables associated with caffeine withdrawal (Juliano & Griffiths, 2004).

The present study examined prevalence rates of caffeine use in males and females, and investigated potential predictors of caffeine-related withdrawal symptoms in college freshmen.

Specifically, this study examined the extent to which certain environmental factors contribute to risk for caffeine withdrawal in a sample of caffeine using college students.

The study utilized the first year (Fall, 2011) freshman cohort of the VCU Spit for Science Survey (Dick & Kendler; NIH R37 AA011408). This unique dataset contains survey information from 2056 participants about recent caffeine use, as well as use of alcohol and other substances, personality measures, and other emotional and behavioral symptoms (Dick et al., 2014). Statistical analyses were used to identify potential demographic and psychosocial variables associated with having caffeine withdrawal headaches (p <.25) to determine which of these variables, in combination with caffeine use measures, best predict caffeine withdrawal headache. Direct univariable and multivariable logistic regression analysis were then used to provide a parsimonious model for predicting caffeine withdrawal headaches.

Together, this information added to the validity of self-report frequency measures of caffeine consumption by examining their relationship to the experience of caffeine withdrawal headache, which provided insight regarding the efficiency and accuracy of self-report assessments of caffeine use. This investigation also provided evidence which may inform practitioner ability to identify persons at greatest risk for negative consequences of caffeine dependence, including withdrawal.

Physical and Chemical Properties of Caffeine

Caffeine (M_r 194.19), also systematically called 1,2,7-trimethylxanthine, 1,3,7-trimethyl-2,6-dioxopurine or 3,7-dihydro-1,3,7-trimethyl-1-H-purine-2,6-dione, was discovered during the period 1820-1827 and belongs to a class of methylxanthines, which are defined as purine alkaloids. At room temperature caffeine consists of an odorless, bitter, white powder with a density of 1.23 ($d^{18}/_4$), but may also consist of flexible, silky needles upon crystallization from

water (Arnaud, 1999; Tarka & Hurst, 1998). Caffeine's chemical formula is $C_8H_{10}N_4O_2$ (Weinberg & Bealer, 2001).

Caffeine occurs naturally in a variety of foods, seeds, plant species, and beverages (e.g., coffee, tea, chocolate, kola nuts), with the highest caffeine concentrations found in guarana seeds (*Paulinia cupana*), followed by tea leaves (*Camellia thea, C. sinensis*), and then coffee beans (*Coffea arabica*). Additionally, caffeine has been discovered in more than sixty other plant species worldwide **(**Arnaud, 1999; Barone, & Roberts, 1996; IFIC 2008). Pure caffeine is chemically extracted by a number of methods including the decaffeination process of coffee and black or green tea, as well as biosynthesis, methylation, and total chemical synthesis of other methylxanthines (theophylline and theobromine) (Arnaud, 1999; Tarka & Hurst, 1998; Weinberg & Bealer, 2001). Caffeine's physical and chemical properties are described in Table 1.

Table 1.

Physical and Chemical Properties of Caffeine.

Property	Value
Molecular weight	194.19g
Melting Point	234-239^{0}C
Sublimation point	178^{0}C
Specific gravity	1.2
Volatility	0.5%
Solubility (in water)	2.2%
Vapor pressure (at 178^{0}C)	760 mm Hg
Vapor density	6.7
pH (1% solution)	6.9
Median lethal dose	150-200 mg kg^{-1}

From Arnaud, 1999; Mumin, Akhter, Abedin, & Hossain, 2006; Tarka & Hurst, 1998

Pharmacology of Caffeine

Pharmacokinetics

After oral ingestion, caffeine is rapidly and completely absorbed from the gastrointestinal track, with peak blood levels occurring 45 – 60 minutes following oral doses of 5-8 mg per kilogram of body weight and yield peak plasma concentrations of 8 to 10 mg/l (Bonatie, Latini, Galletti, Young, Tognoni, & Garattini, 1982; Griffiths, Juliano, & Chausmer, 2003). Therefore, one cup of coffee, which contains a dose of 0.4 to 2.5 mg/kg, provides an estimated peak concentration of 0.25 to 2 mg/l or approximately 1 to 10 μM (Fredholm, Bättig, Holmén, Nehlig, & Zvartau, 1999).

Caffeine is quickly eliminated with a typical half-life of 3 – 6 h. (Arnaud, 1999; Benowitz, 1998; Juliano & Griffiths, 2004) and is metabolized by the demethylation to dimethylxanthines, with the primary metabolites being paraxanthine, theobromine and theophylline (Benowitz 1990; Griffiths, Juliano, & Chausmer, 2003; Spiller, 1998; Weinberg & Bealer, 2001). Ring hydroxylated urates and acetylated uracil also account for a portion of caffeine metabolism. Caffeine's metabolism mostly occurs in the liver via catalysis by the cytochrome P450 1A2 (CYP1A2) enzyme and by the catalytic action of CYP2E1, the ethanol-inducible CYP (Carrillo & Benitez, 2000; Gu, Gonzalez, Kalow, & Tang, 1992; Juliano, Ferré, & Griffiths, 2014).

Various environmental, biological and gender-based factors are known to modify the rate at which caffeine is metabolized. For instance, females metabolize caffeine 20 to 30% faster than males (Nawrot, Jordan, Eastwood, Rotstein, Hugenholtz, & Feeley, 2003; Weinberg & Bealer, 2001). Additionally, cigarette smoking increases the elimination of caffeine (Arnaud, 1999; Brown, Jacob, Wilson, & Benowitz, 1988; Weinberg & Bealer, 2001) by decreasing

caffeine's half-life by 30-50% and doubles the rate at which caffeine is eliminated (Fredholm et al., 1999). Conversely, obesity, alcohol consumption, and chronic liver disease decrease caffeine elimination rate (Arnaud, 1999; Benowitz, 1990; Weinberg & Bealer, 2001). Also, decreased caffeine elimination is reported in both pregnant women and those who are taking oral contraceptives (Arnaud, 1999). Genetic polymorphisms in the CYP1A2 enzyme are also associated with different rates of caffeine metabolism, which will be discussed further.

Urinary excretion is the main elimination route of caffeine, with only 2-5% of ingested caffeine being excreted through feces (Arnaud, 1999; Benowitz, 1990), and only 10% of caffeine is excreted unchanged (Julian, Advokat, & Comaty, 2011).

Mechanism of Action

Caffeine is a central nervous system (CNS) stimulant (Arnaud, 1999) and research has identified three biochemical mechanisms that help to explain the pharmacological and physiological properties of caffeine. The primary mechanism of action of caffeine, and the most recently studied mechanism, is the competitive antagonism at A_1, A_2, and A_3 adenosine receptors (Arnaud, 1999; Benowitz, 1998; Fison, Borgkvist, & Usiello, 2004; Fredholm et al., 1999). These receptors are found in the brain, adipose tissue cardiovascular, respiratory, renal, and gastrointestinal systems, and are classified as a neuromodulator, which influences the release of various neurotransmitters in the CNS (Julien et al., 2011). Additionally, they promote lipolysis, platelet aggregation, are inotropic and chronotropic to the heart, and cause bronchodilation and diuresis (Arnaud, 1999).

According to this mechanism, caffeine non selectively blocks both adenosine receptors and competitively inhibits the actions of adenosine. At the presynaptic level, adenosine inhibits neuronal release of acetylcholine and other neurotransmitters such as norepinephrine, dopamine,

gamma amino butyric acid (GABA), and serotonin. Therefore caffeine's ability to block adenosine's inhibitory affect contributes to the release of these neurotransmitters (Benowitz, 1990; Daly & Fredholm, 1998; Nehlig, Daval, & Debry, 1992), and also "increases circulating catecholamines consistent with reversal of the inhibitory effects of adenosine on these systems" (Benowitz, 1990, p. 279; Griffiths et al., 2003; Nehlig et al., 1992). Strong experimental evidence exists supporting that the adenosine modulation of dopaminergic neurotransmission in the brain is what plays a key role in the psychostimulant effects of caffeine, a similar mechanism involved with classical psychostimulants (Fison et al., 2004; Juliano et al., 2014).

It has also been suggested that caffeine's ability to inhibit cyclic nucleotide phosphodiesterase might contribute to the discriminative stimulus effects of caffeine (Griffiths & Mumford, 1996; Weinberg & Bealer, 2001). According to this mechanism, caffeine is known to increase cyclic adenosine 3',5'-monophosphate (cAMP) concentrations in various tissues, while phosphodiesterase catalyzes the breakdown of cAMP concentrations. However, because most selective phosphodiesterase inhibitors are behavioral depressants, it is unlikely that phosphodiesterase inhibition would be involved in low-dose caffeine discriminative effects. Moreover, there are mixed results implicating phosphodiesterase inhibition being involved in the discriminative effects of higher caffeine dose as well (Griffiths & Mumford, 1996). Furthermore, the caffeine concentrations required for this mechanism are produced only with millimolar concentrations (i.e., toxic concentrations) and therefore, further research is needed to conclude that this mechanism significantly contributes to the *in vivo* pharmacology of moderate caffeine doses (Debry, 1994).

The third mechanism of action is the effect of methylxanthines on the mobilization of intracellular calcium from skeletal, cardiac, and neuronal tissue (Carrillo & Benitez, 2000;

Debry, 1994). At certain concentrations caffeine lowers the excitability threshold and prolongs the duration of muscle contraction by promoting translocation of calcium through the plasma membrane and the sarcoplasmic reticulum. A minimum concentration of 250 μM of caffeine is necessary to produce effects of calcium shifts, while plasma concentrations of caffeine after ingestion of coffee is usually less than 100 μM; therefore, this mechanism of action is also not representative of an essential mechanism of caffeine in the CNS (Debry, 1994).

Physiological & Behavioral Effects of Caffeine

As a CNS stimulant, caffeine produces a number of physiological effects, in addition to a number of positive cognitive and affective effects (Fredholm et al., 1999; Meredith, Juliano, Hughes, & Griffiths, 2013; Smith, 2002). Such effects of caffeine are generally dose dependent and can produce a variety of positive and negative physiological health effects, impacting the cerebral vascular system, cardiovascular system (e.g., increasing blood pressure and low-density lipoproteins), neuroendocrine system, renal system, respiratory system, hepatic, and gastrointestinal systems (Arnaud, 1999; Griffiths et al., 2003; Juliano et al., 2014; Nawrot et al., 2003; Smith, 2005; Wolk, Ganetsky, & Babu, 2012). However, scientific evidence suggests that among the healthy adult population, moderate daily caffeine consumption (400-450 mg/day, or about 5.7 mg/kg body weight per day for a 70-kg person, equivalent to four or fewer cups of coffee per day) is not associated with adverse health effects (Heckman, Weil, & De Mejia, 2010; Nawrot et al., 2003).

In humans, the subjective and discriminative stimulus effects of caffeine at low to moderate doses (20 – 400-450 mg/day) can be characterized by an overall increase in arousal. These arousal effects have been characterized as an increase in frequency of positive mood self-reports (e.g., sense of wellbeing, happiness) (Griffiths et al., 2003; Juliano et al., 2014), energy

(e.g., stimulating locomotor activity), alertness, reduced fatigue, attention, sociability, and certain complex cognitive functioning (i.e., mental performance in work settings) (Arnaud, 1999; Griffiths & Mumford, 1996, 2000; Juliano & Griffiths, 2004; Winston et al., 2005).

Furthermore, caffeine is associated with increased vigilance (Silverman, Mumford, & Griffiths, 1994) and sustained response, reduced depressive symptoms, and decreases in the risk of suicide (Penolazzi, Natale, Leone, & Russo, 2012). Additionally, caffeine acts as an ergogenic aid (Lamarine, 1998), and caffeine consumption enhances information processing, memory performance, and psychomotor functioning, such as: improvement of delayed recall, recognition memory, semantic memory, verbal memory, and visual selection and fine motor control (Jarvis, 1993; Smith & Tola, 1998). The profile of these effects are similar to that of other psychostimulants, such as cocaine, where in an experimental study approximately 300 mg/70 kg of caffeine was shown to produce similar stimulant effects similar to that of 25 mg of cocaine (Rush, Sullivan, & Griffiths, 1995).

Caffeine has also been characterized as a therapeutic agent and is associated with improved glucose tolerance and subsequent reduced risk of type II diabetes, weight loss, lowered risk for incidence of Parkinson's disease and improvement in Parkinson's symptoms, reduced risk for some types of cancer at several anatomical sites, in addition to treatment for post-surgical withdrawal headaches and migraine headaches (Butt & Sultan, 2011; Floegel, Pischon, Bergmann, Teucher, Kaaks, & Boeing, 2012; Higdon & Frei, 2006; Juliano et al., 2014; Sinha, Cross, Daniel, Graubard, Wu, Hollenbeck, Gunter, Park, & Freedman, 2012).

Alternatively, higher and excessive doses (acute doses ≥ 200 mg in non-habitual users, or habitual daily use > 500 – 600 mg, approximately four to seven cups of coffee or seven to nine cups of tea) can lead to dysphoric feelings of anxiety, jitteriness, restlessness,

irritability/aggression, tinnitus, muscle twitching, palpitations, headaches, upset stomach, and other health risks (Arnaud, 1999; Griffiths & Mumford, 1996; Griffiths et al., 2003; Heckman, et al., 2010; Nawrot et al., 2003; Smith & Tola, 1998; Chait & Griffiths, 1983; Charney, Galloway, Heninger, 1984; Loke, 1998; Oliveto, Bickel, Hughes, Terry, Higgins, & Badger, 1993; Reissig, Strain, & Griffiths, 2009).

Additional behavioral effects resulting for CNS stimulation include a delay in sleep onset, and impaired sleep quality characterized by an increased number of spontaneous awakenings and body movements, which results in decreased total sleep time (Alford, Bhatti, Leigh, Jamieson, & Hindmarch, 1996; Arnaud, 1999; Hinmarch, Rigney, Stanley, Quinlan, Rycroft, & Lane, 2000). Administration of higher doses of caffeine has led to significant number of caffeine users who consume caffeine regularly endorsing dependence/abuse criteria and meeting criteria for "caffeinism," a psychophysiological syndrome first described in the American Psychiatric Association's (APA) Diagnostic and Statistical Manual of Mental Disorders, Third Edition – Revised (DSM-III-R, APA, 1987), also known as acute or chronic Caffeine Intoxication in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV, APA, 1994), in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition – Text Revised (DSM-IV-TR, APA, 2000), and also in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5, APA, 2013) (Arnaud, 1999; Griffiths & Mumford, 2000; Hughes Oliveto, Liguori, Carpenter, & Howard, 1998; Weinberg & Bealer, 2001).

Dietary Sources of Caffeine

There is a current proliferation of caffeinated food and beverage products within the U.S. and around the world. The amount of caffeine in these products varies depending on a number

of factors, including serving size and type of product. For example, an eight-ounce cup of brewed coffee typically has 65-120 mg caffeine; an eight-ounce serving of brewed tea has 20-90 mg, and a 12- ounce canned soft drink has 30-60 mg (Julien et al., 2011; Knight, Knight, Mitchell, & Zepp, 2004). However, an eight-ounce cup of coffee from Starbucks can contain up to 165 mg caffeine (Mayo Clinic, 2014) and it is estimated that coffee is higher in caffeine content than tea by approximately 60 to 70% (Lundsberg, 1998), and chocolate or cocoa confectionery products usually contain the least amount of caffeine (see Table 2) (IFIC, 2008).

The average caffeine contents of various foods and beverages are presented in Table 2, and are reported in milligrams. However, to create a standard measure of caffeine intake for individual consumers, caffeine intakes (in mg) are converted to a body weight basis (mg/kg body weight) based on the actual weights of each individual, and therefore, an individual's caffeine intake is commonly reported in mg kg^{-1} (Barone & Roberts, 1996). For example, an average 8 – 12 oz. cup of coffee contains approximately 100 – 200 mg of caffeine (Juliano et al., 2014; Julien et al., 2011; Weinberg & Bealer, 2001), and a dose level up to 400 mg day^{-1} is equivalent to 6 mg kg^{-1} body weight day^{-1} in a 65-kg person, or 143.3 lbs. person (Nawrot et al., 2003).

Table 2.

Average Caffeine Content of Common Foods and Medications.

Beverages & Foods (volume or weight)	Avg. caffeine (mg)
Coffee	
Brewed/drip (12 oz.)	200
Instant (12 oz.)	140
Espresso (1oz.)	70
Tea	
Instant tea (6 oz.)	30
Brewed tea (6 oz.)	40

Cola Drinks	
Coca-Cola Classic (12oz.)	33
Mountain Dew/Diet Mountain Dew (12oz.)	55
Pepsi Max/Diet Pepsi Max	69
Energy Drinks/Shots	
Red Bull Energy Drink (8.4oz.)	78
5-Hour Energy (shot; 2oz.)	207
Other	
NoDoz, Max. Strength (1 tab)	200
Excedrin, Extra Strength (2 tabs)	30
Foosh Energy Mints (1)	100
Jolt Gum (1 piece)	33
Hersey's Kisses (9 pieces)	9

Juliano et al., 2014

More recently, much attention has focused on other caffeinated beverages, such as energy drinks and energy shots, which have become a common source of caffeine worldwide and in the United States (U.S.) (Reissig et al., 2009). First introduced in the USA in 1997, the market and consumption for these beverages has grown exponentially. For example, from 2002 to 2006 the estimated total U.S. retail market value for energy drinks was $5.4 billion, with nearly 200 brands launched in U.S. in just a 12-month period ending in 2007 (Reissig et al., 2009). Together, sales of caffeinated energy drinks and shots rose 60% in the United States between 2008 and 2012 to $12.5 billion/year. Sales are expected to grow at a similar rate until reaching $21.5 billion/year in 2017 (Packaged Facts, 2013).

While the U.S. Food and Drug Administration (FDA) has limited the caffeine content of sodas to 65 mg per 12 oz. (18 mg/100 mL), energy drinks are not currently subject to the same FDA regulations (McCusker, Goldberger, & Cone, 2006) since they are marketed as dietary supplements, and they often contain high amounts of caffeine compared to other caffeinated beverages (Arria & O'Brien, 2011). Therefore, the safety standards concerning these beverages are made solely by the manufacturers, and their only requirement is to include caffeine on the

ingredient list (U.S. FDA, 2013). It is difficult to determine the caffeine content in these beverages, but reported amounts vary widely (see Table 2), with the caffeine content and concentration ranging from 80-120 mg per eight-ounce serving (American Beverage Association, 2009) and up to a startling 505 mg per in a 24-ounce can (the equivalent of 14 cans of soda or several cups of coffee) (Reissig et al., 2009). The most popular caffeinated energy drinks in the U.S. are called Red Bull (Red Bull GmbH), Amp (PepsiCo, Inc.), Monster (Monster Beverage Company), Rock Star (Rockstar Inc.), Vault (Coca-Cola Company), and FullThrottle (Coca-Cola Company).

These beverages also contain caffeine from guarana and other added sources with unknown safety profiles, such as: taurine, riboflavin, pyridoxine, niacin, glucuronolactone, L-Carnitine, nicotinamide, other B vitamins, and various herbal derivatives not normally announced as caffeine (Aranda & Morlock, 2006; Higgins, Tuttle, & Higgins 2010; IFIC 2008; Wolk et al., 2012).

Similar to caffeinated energy drinks, an emerging and more accessible form of caffeine has been developed in the form of "energy shots." These "shots" claim to produce similar beneficial mental and/or physical energy effects as any other caffeinated beverage but are generally only 59-88 milliliters in volume. They can contain 80-140 mg of caffeine and a blend of other ingredients comparably found in energy drinks (B vitamins, taurine, glucuronolactone, etc.). Additionally, this alternative form of caffeinated beverage has taken on a variety of flavor combinations and product line extensions that are appealing to a diverse set of consumers, which has led to markedly impressive sales (Peterson, 2013). Furthermore, these beverages have become a particular trend among athletes, as they are believed to be a possible pre-competition supplement given caffeine's stimulating effects (Heckman et al., 2010; Nawrot et al., 2003;

Schubert, Astorino, & Azevedo, 2013). Additionally, numerous studies have documented that young adults, teenagers, college students, and military personnel (Heckman, Sherry, & de Mejia, 2010; Lieberman, Stavinoha, McGraw, White, Hadden, & Marriott, 2012; Norton, Lazev, & Sullivan, 2011) are commonly consuming these caffeinated beverages.

In addition to caffeine occurring in a number of foods and beverages, caffeine is also an active ingredient in a number of over-the-counter and prescription compounds, including antidrowisness pills, non-drowsy cold remedies, pain relief tablets, and weight-loss pills given caffeine's appetite suppressant and analgesic effect. Caffeine is even added to some commercial water, mints, candy, chewing gum, potato chips, ice cream, and oatmeal (Barone & Roberts, 1996; IFIC, 2008; Julien et al., 2011; Temple, 2009; Lundsberg, 1998; Weinberg & Bealer, 2001). Substances called "energy sheets" (PureBrands, Boca Raton, FL, USA), sheets of paper that contain 100mg of caffeine per serving and are made from dissolvable pieces of paper that are placed on the tongue (Wolk et al., 2012) are also available.

Epidemiology

Caffeine Consumption World Wide

The markedly different and broad vehicles of caffeine self-administration, along with the widely different social/culture/population contexts caffeine is consumed (e.g. tea/coffee breaks in the United Kingdom, U.S., Europe, and Asia) and kola nut chewing in Nigeria (Barone & Roberts, 1996; Frary et al., 2005; Knight, et al., 2004; Lundsberg, 1998; Weinberg & Bealer, 2001), has made caffeine one of the most researched substances, however, there is a lack of population-level empirical data on caffeine intakes around the world (Meredith et al., 2013) and most studies cite information dating back to the 1990s. For example, Barone and Roberts (1996) collected information from available product usage data and food consumption survey data and

estimated the mean daily caffeine intake in the United Kingdom to be at 4 mg kg^{-1} for adult consumers. In Denmark, caffeine intake is reported to be the highest among adults with 7.0 mg kg^{-1}, whereas African countries like Algeria, Nigeria, and Tanzania consume some of the lowest levels at 4 and 7 mg/person/day, respectively (< 1.0 mg kg^{-1}) (Fredholm, et al., 1999).

Caffeine Consumption in the U.S.

Caffeine consumption is equally ubiquitous in much of North America, with 80-90% of U.S. adults reporting use (Drewnowski & Rehm, 2016; Frary et al., 2005; Fulgoni et al., 2015; Lundsberg, 1998; Mitchell et al., 2014; Meredith et al., 2013). The most common sources of caffeine include coffee, soft drinks, and tea (Drewnowski & Rehm, 2016; Barone & Roberts, 1996; Frary et al., 2005; Fulgoni et al., 2015; Somogyi, 2010). Comprehensive population-level data on caffeine intake in the U.S. is quite limited (Ahuja, Goldman, & Perloff, 2006; Frary et al., 2005; Knight et al., 2014; Mitchell et al., 2014), with data often cited from the 1980's and 1990's, with the most current data being from the year 2012 (Drewnowski & Rehm, 2016).

For example, based on the 1989 Market Research Cooperation of America, the mean daily caffeine consumption was reported to be approximately 3 mg kg^{-1} in the US general population and 4 mg kg^{-1} in adult U.S. consumers (Barone & Roberts, 1996). Furthermore, in 1994 Debry found individuals in the US general population aged 1-5, 6-11, 12-17, & 18+ consumed 1.20, 0.85, 0.74, and 2.60 mg kg^{-1} of caffeine daily, respectively, from combined sources of caffeine including coffee, tea, soft drinks, & chocolate. Debry (1994) also found that for individuals aged 18+, in the United States of American, coffee was the primary source of daily caffeine consumption (80.7%), compared to tea, soft drinks and chocolate, while tea outsourced soft drinks and chocolate as the primary source of daily caffeine consumption (48.2%) for individuals aged 6-11 and 12-17 (45.9%).

In 2005, Frary and colleagues published caffeine intake data from a representative sample of the U.S. population using the U.S.D.A 1994 to 1996 and 1998 CSFII (sample *N* = 18,081; caffeine consumers *N* = 15,716; ages 2-54 years). They found eighty-seven percent of the entire sample of caffeine users consumed food and beverages containing caffeine, with an average of 193 mg caffeine per day and 1.2 mg kg^{-1} per day. Frary et al., (2005) also found that men and women aged 35 to 64 years were among the highest consumers of caffeine (336 mg/day) and that caffeine consumption was positively correlated with increases in age (among people aged 2 to 54 years). Major sources of caffeine were coffee (71%), soft drinks (16%), and tea (12%), with coffee as the major source of caffeine among adults and soft drinks were the primary source for children and teens.

In 2004, data were reported by Knight and colleagues using the 1999 US Share of Intake Panel (beverage survey) (*N* = 10,712 caffeine consumers). The authors found per capita consumption level of caffeine for all consumers (of all ages) in the US general population to be approximately 120 mg per day, or a mean intake of 1.73 mg kg^{-1} per day. This data suggests that mean caffeine intake has decreased over the years, and is within recommended safe levels, where moderate amounts of caffeine are generally considered to be 400–450 mg/day (5.7–6.4 mg kg^{-1}) (Nawrot et al., 2003). In regards to heavier US caffeine consumers, Knight et al., (2004) found that caffeine intake at the 90th percentile was 287 mg/day or 4.03 mg kg^{-1} per day, which has also decreased from the mean daily caffeine intake of 5-7 mg kg^{-1} for heavier consumers (90th percentile) reported by Barone and Roberts (1996).

The most recent available literature on caffeine intake and its primary sources rely heavily rely on nationally representative samples. Two primary surveys are what provide key sources of newer quantitative data on caffeine intake. They are the Kantar Worldpanel (KWP)

Beverage Consumption Panel (formerly the Share of Intake Panel), and the National Health and Nutrition Examination Survey (NHANES), which monitors the nation's nutrition data (Ahluwalia & Herrick, 2015).

The KWP beverage consumption survey involves a U.S. representative sample and provides population-based estimates of beverage consumption by using a 7-day diary recorded by participants over the Internet. Respondents recorded details regarding their caffeine consumption, such as type, brand, preparation, location (home or away from home), and amount of all beverages consumed. To be able to describe caffeine consumption in relation to body weight (mg kg^{-1}), information on height, weight, and demographic characteristics was also collected at the same time (Ahluwalia & Herrick, 2015; Mitchell et al., 2014).

The NHANES is a series of large, stratified, multistage surveys of the U.S. civilian, conducted by the National Center for Health Statistics, CDC (Ahluwalia & Herrick, 2015). Since 1999, the NHANES has been conducted annually and data are publicly released every 2 years for approximately 10,000 individuals. Participants are administered a series of questionnaires asking for details on the type and quantity of all foods and beverages consumed in a 24-h period (Ahluwalia & Herrick, 2015).

In 2015, Fulgoni and colleagues, using the NHANES (2001 to 2010), examined dietary intake of caffeine from all caffeine-containing foods and beverages (excluding dietary supplements and medicines) for adults ≥19 years of age (N = 24,808). The authors estimated that 89% of the adult U.S. population consumes caffeine on any given day, with an equal percentage of men and women consuming caffeine. Among caffeine consumers, intake at the 90th percentile has increased to 436 mg/day, and 99th percentile of intake was estimated at 1066 mg/day. This is contrary to what Knight et al. (2004) found when the highest caffeine intakes

were below this recommended level (Knight et al., 2004). The authors also estimated that among caffeine consumers, the mean intake of caffeine was 161 mg/day for those aged ≥19 years, with men having a higher average intake, 211 mg/day, compared with females who consumed on average 183 mg/day. Overall, caffeine consumption was highest in males aged 31–50 years and lowest in females aged 19–30 years (Fulgoni et al., 2015).

More recently, Mitchell and colleagues (2014), reported on 2010-2011 U.S. population data about consumption of caffeinated beverages from the Kantar Worldpanel (KWP) Beverage Consumption Panel. Of the 42,851 respondents aged ≥2 years (N = 37,602 caffeine consumers), approximately 85% of the U.S. population reported consuming at least one caffeinated beverage and over 98% of all beverages consumed came from coffee (specialty coffee drinks, iced coffee, brewed, instant, and decaffeinated coffee, tea (e.g., green tea, white tea and other varieties, iced tea), caffeinated/carbonated soft drinks, and energy drinks (other beverages included chocolate drinks, and energy shots). Coffee accounted for eighty percent of all caffeine consumed.

Overall, caffeine intakes from all caffeinated beverages were 380 mg/day or 5.0 mg kg^{-1} at the 90th percentile in all ages, and caffeine intakes at this percentile remained slightly above 400 mg/per day for adults aged ≥35 years (420-467 mg/day or 5.1–5.7 mg kg^{-1}). Among caffeine consumers ages 18-24 years, the mean caffeine intake of coffee was approximately 130 mg/day. Also among caffeine consumers, coffee drinkers consumed the most caffeine with the highest mean amount of caffeine (223 mg/day) ingested by adults aged 50–64 years (Mitchell et al., 2014). The percentage of energy drink consumers across all age groups was surprisingly low (4.3%) and accounted for less that 2% of the total daily mean caffeine among all caffeinated beverage consumers. However, the greatest proportion of caffeinated beverage consumers consuming energy drinks were teenagers, ages 13-17 years and young adults, ages 18-24 years,

the groups central to most of caffeinated energy drink consumption patterns (Mitchell et al., 2014). In conclusion, Mitchell and colleagues (2014) found that among adult caffeine consumers in the U.S., the mean daily caffeine consumption was estimated at 165 mg/day, the equivalence to about three 6-oz cups of coffee or five 16-oz bottles of cola soft drink (Barone & Roberts, 1996; Griffiths et al., 2003; Juliano, et al., 2014).

The latest study conducted by Drewnowski & Rehm (2016) using the most recent NHANES 2011-2012 data (N = 24,808) estimated adult (≥20 years) caffeine consumption to be 196 mg/day for men and 151 mg/day for women, numbers that slightly deviate from what Fulgoni and colleagues (2015) estimated. For adults, Drewnowski & Rehm (2016) found caffeine consumption to be lowest in the non-Hispanic black population and highest in the non-Hispanic white population. The authors reported that overall, among both children (ages 4-19 years) and adults (≥20 years), caffeine intake has declined from 175 mg/day in 1999–2000 to 142 mg/day in 2011–2012, with the largest drop in caffeinated soda consumption (41 mg/day to 21 mg/day). For adults specifically, caffeine intake decreased from 217 mg/day to 173 mg/day, also attributed by a marked decrease in caffeine from soda (from 43.9 mg/day to 23.0 mg/day); there was no evidence of an increase in caffeine from coffee or tea (Drewnowski & Rehm, 2016). Among adults, caffeine from energy drinks increased significantly from zero in 1999–2000, to 0.31 mg/day in 2003–2004, and 2.9 mg/day in 2011–2012; however, when considering these trends, there was still evidence of a decline in caffeine consumption overall. Beverages continued to be the bulk of caffeine consumed, and coffee, tea, and soda remain predominate sources, while energy drinks accounted for 2% of caffeine (2.7 mg/day) and foods contributed 2.0 mg/day or 1.5% of total caffeine (Drewnowski & Rehm, 2016; Fulgoni et al., 2015; Mitchell et al., 2014).

Because energy drinks and energy shots were fairly new in 1999, the aforementioned population-level studies conducted by Barone & Roberts, (1996), Knight et al., (2004), and Frary et al., (2005) did not include these caffeinated beverages as a category. The increased popularity of energy drinks has led them to become a major source of caffeine consumption, especially among adolescents and young adults (Babu, Church, & Lewander, 2008; Seifert, Schaechter, Hershorin, & Lipshultz, 2011; Temple, 2009). In addition to the above data examining energy drink consumption patterns, Branum, Rossen, & Schoendor (2014) found caffeine intake from energy drinks in those aged 19-22 years, based on the NHANES 1999-2010 data, to be an estimate of 10%. Moreover, Bailey, Saldanha, & Dwyer (2014) estimated that 3% of the U.S. population (age ≥1 years) use caffeine-containing energy products after examining data from the NHANES (2007-2010; N = 19, 142). The authors also reported the highest usage of these products was among males between the ages of 19 and 30 years (7.6%), corroborating the data reported by Mitchell et al., (2014). Furthermore, data from a 2012 cross-sectional survey of adolescents attending public schools (grades 7th through 12th) in Atlantic Canada found that 62% reported consuming caffeinated energy drinks at least once in the past month, and approximately 20% reported use once or more per month (Azagba, Langille, & Asbridge, 2014). It is also estimated that 30% of high school students consume energy drinks, and 51% of college students consume greater than one energy drink each month (Malinauskas, Aeby, Overton, Carpenter-Aeby, & Barber-Heidal, 2007; Terry-McElrath, O'Malley, & Johnston, 2014). These results are similar those reported in studies of energy drink use among college students (Arria, Caldeira, Kasperski, O'Grady, Vincent, Griffiths, & Wish, 2010; Buxton & Hagan, 2012; Hoyte, Albert, & Heard, 2013; Miller, 2008a; Norton et al., 2011; Velazquez, Poulos, Latimer, & Pasch, 2012). However, both Arria et al., (2011) and Miller, (2008a) reported that 10% of college students

were "weekly" consumers, while Skewes, Decou, & Gonzalez, 2013 reported higher estimates for weekly consumption (39.2%).

The most recent data examined by Arria, Bugbee, Caldeira, &Vincent (2015) using the National Institutes of Health-funded Monitoring the Future (MTF) Survey (2010 and 2011 surveys), found that 35% of eighth graders and 29% of both tenth and twelfth graders reported energy drink consumption. Eighth graders were also most likely to report daily use for energy drinks (18%) (Arria et al., 2015). Further, for every grade, males were more likely than females to use energy drinks. African American individuals had the lowest prevalence of energy drinks use regardless of grade, and the highest prevalence was observed among Hispanic eighth graders (43%), and the lowest among African American twelfth graders (19%) (Arria et al., 2015).

Overview of Caffeine and Caffeine Dependence

Reinforcing Properties of Caffeine

The reinforcing efficacy of a drug is dependent on the delivery of the drug and its related effectiveness in establishing or sustaining behavior (Griffiths & Mumford 2000, 1996). A number of laboratory animal and human studies have been published focused on reinforcing effects of caffeine. In a review of this literature, Griffiths & Mumford (2000) & Griffiths et al., (2003) found a number of intravenous caffeine self-injection studies in laboratory animals affirmed that caffeine can function as a reinforcer under certain conditions. However, the findings from such research also suggested that caffeine's reinforcing ability is more analogous to that of self-injection studies of nicotine as compared to other stimulants (e.g., amphetamines and cocaine).

The reinforcing effects of caffeine have also been found in human laboratory studies. Numerous studies using various subject populations (moderate and heavy caffeine users with and

without histories of alcohol or drug abuse); various methodological approaches (variations on choice and ad libitum self-administration procedures), and different caffeine vehicles (coffee, soda or capsules), and various contexts of different behavioral requirements after drug ingestion (vigilance vs. relaxation activities) positively suggested that caffeine could function as a reinforcer in humans (Evans, Critchfield, & Griffiths, 1994; Hale, Hughes, Oliveto, & Higgins, 1995; Hughes, Higgins, Bickel, Hunt, Fenwick, Gulliver, & Mireault, 1991; Hughes, Hunt, Higgins, Bickel, Fenwick, & Pepper, 1992a; Hughes, Oliveto, Bickel, Higgins, & Valliere, 1992b; Hughes, Oliveto, Bickel, Higgins, Badger, & Gary, 1995, Garrett & Griffiths, 1998; Griffiths & Mumford, 1995, 1996, 2000; Griffiths, Bigelow, & Liebson, 1986a, 1989; Griffiths, Bigelow, Liebson, O'Keefee, O'Leary, & Russ, 1986b, 1986b; Griffiths et al., 2003; Griffiths & Woodson, 1988a, 1988b; Lieuori & Hughes, 1997; Liguori, Hughes, & Oliveto, 1997; Mitchell, de Wit, & Zacny, 1995; Oliveto, Hughes, Higgins, Bickel, Pepper, Shea, & Fenwich, 1992a; Oliveto, Hughes, Pepper, Bickel, & Higgins, 1990; Silverman, Mumford, & Griffiths, 1994; Schuh & Griffiths, 1997). It has been demonstrated that caffeine reinforcement occurs in approximately 45% of normal subjects with histories of moderate and heavy caffeine use (Griffiths & Woodson, 1988a, Hughes, Oliveto et al., 1993; Evans, et al., 1994; Silverman et al., 1994; Hale et al., 1995; Liguori & Hughes, 1997; Liguori et al., 1997).

This extensive body of research has also shown that caffeine reinforcement follows an inverted U-shaped function in relation to dose (Griffiths & Mumford, 1996, 2000; Griffiths et al., 2003). That is, the reinforcing effect of caffeine appears to be stronger when low doses (25mg per cup of coffee and 33 mg per serving of cola) are self-administered repeatedly throughout the day (Hughes, et al., 1992a; Oliveto, et al., 1995; Liguori et al., 1997), while increasing doses beyond 50mg or 100mg decrease caffeine self-administration rates and caffeine choice (e.g.,

coffee, soda, or capsules) (Griffith et al., 1986b; Griffiths & Woodson, 1988a; Hughes et al., 1992b; Stern, Chait, & Johanson, 1989). Moreover, high doses of caffeine (e.g., 400mg or 600mg single doses) have been shown to produce caffeine avoidance (Griffiths & Woodson, 1988a). Overall, both the available animal and human research suggests that caffeine is a reliable reinforcer, but the evidence claims caffeine to be a less robust reinforcer than other psychoactive stimulants, such as cocaine or *d*-amphetamine, and instead is more similar to nicotine (Griffiths & Mumford, 2000).

Caffeine Intoxication

Historically, few studies have examined the prevalence of caffeine's potential to cause adverse effects or clinically significant distress (i.e., caffeine intoxication) in the general population. Case reports, however, did exist indicating incidences of caffeine intoxication; therefore, the *DSM-III-R* (1987) Task Force recognized that acute and/or chronic caffeine use can result in caffeine toxicity, and the syndrome Caffeine Intoxication, or *caffeinism*, was first recognized as a syndrome in the *DSM-III-R* (1987) (Griffiths et al., 2003; Juliano et al., 2014).

The Diagnostic and Statistical Manual of Mental Disorders has continued to recognize the clinical importance of these effects and have included the diagnosis of acute or chronic Caffeine Intoxication (*DSM-IV-TR*, 2000*; DSM-5*, 2013). This diagnosis must be indistinguishable from medical and/or mental conditions, and is manifested by restlessness, nervousness, excitement, insomnia, flushed face, diuresis, gastrointestinal disturbance, and other somatic complaints (Griffiths & Mumford, 2000), which emerge in response to recent consumption of caffeine.

Moreover, patients may experience chronic or recurrent forms of *caffeinism* without recognizing the administration of caffeine-containing beverages and foods as problematic and

therefore may seek treatment for anxiety, insomnia, cardiovascular, gastrointestinal, or other medical/mental conditions (Greden & Walters, 1992). This diagnosis as a category may occur in about 7% of the population (Greden & Walters, 1992; Hughes et al., 1998), and has been known to occur after recent consumption of caffeine at doses as low as 250mg; however, most instances of caffeine intoxication occur after consumption of much higher dose, such as greater than 500mg (Juliano, Ferré, & Griffiths, 2009). Additionally, with emergence of caffeinated energy drink products and concentrated marketing efforts targeting adolescents and young adults, those whom are less likely to be dependent on caffeine, cases of caffeine intoxication/withdrawal may occur (Juliano et al., 2009). For example, there has been a large increase in the number of emergency department visits between 2005 (1,128) and 2008 and 2009 (16,053 and 13,114 visits, respectively) involving energy drink use and caffeine intoxication (SAMHSA, 2011).

Physical Dependence

Physical dependence upon a drug is defined as "time-limited biochemical, physiological, and behavioral disruptions (i.e., a withdrawal syndrome) upon termination of chronic or repeated drug administration" (p. 330, Griffiths & Mumford, 1996). In humans, clinical evidence of physical dependence on caffeine was sparse (Hughes et al., 1992c). In animal studies, physical dependence upon caffeine has been demonstrated following cessation of chronic caffeine dosing. In rats, a 50%-80% reduction in spontaneous locomotor activity, i.e., lever pressing (Finn & Holtzman, 1986; Holtzman 1983), and a 20%-50% reduction in operant responding (Carney, 1982) were found. Such symptoms of withdrawal have been demonstrated at doses ranging from 6mg/kg per day (Vitiello & Woods, 1977) to 190 mg/kg per day (Boyd, Dolman, Knight, & Sheppard, 1965), and across caffeine dosing frequencies ranging from once daily (Carney, 1982) to several times per day (Holtzman, 1983) (Griffiths & Mumford, 1996). More recently,

preclinical studies of physical dependence on caffeine continued to demonstrate reductions in operant conditioning (Carroll, Hagen, Asencio, & Brauer, 1989; Mumford, Neill, & Holtzman, 1988) and reductions in reinforcing threshold during electrical brain stimulation (Mumford et al, 1988), in addition to significant changes in sleep patterns (Sinton & Petitjean, 1989).

At the human level, scientists estimate that about one-third of the general population may be physically dependent on caffeine. However, caffeine dependence has never been recognized as a mental disorder in the *DSM*. Instead, studies of caffeine dependence have focused on criteria analogous to the *DSM* for other drugs. In a review of this research, Ogawa and Ueki (2007) found four studies that used structured interviews to evaluate subjects using criteria for Substance Dependence. All four studies examined how the *DSM-III-R* or *DSM-IV* criteria for Substance Abuse or Dependence might be applied to caffeine (Hughes et al., 1993; Strain, Mumford, Silverman, & Griffiths, 1994; Hughes et al., 1998; Svikis, Berger, Haug, & Griffiths, 2005).

The first study by Hughes and colleagues (1993) interviewed 162 caffeine users with a structured phone interview and applying DSM Substance Dependence criteria modified to focus on caffeine. They found 44% of current caffeine users (about 36% of the general population sample) met criteria for Caffeine Dependence. Further, this sample included 27% of participants with mild caffeine dependence (three-four criteria), 14% with moderate dependence (five-six criteria), and 3% with severe dependence (seven-nine criteria).

Strain and colleagues (1994) focused on adults who self-identified as psychologically or physically dependent on caffeine and found 59% of subjects met at least three of the following four criteria: desire to cut down, use despite harm, tolerance, and withdrawal. The other criteria were not used (use more than intended; use results in role dysfunction; use despite interpersonal

problems; great deal of time spent with drug, and cravings), as they were deemed inapplicable for a licit drug like caffeine. The third study, conducted by Hughes et al., (1998) found that 30% of current caffeine users sampled in a random digit telephone survey in Vermont endorsed three or more of the seven *DSM-IV* (1994) dependence criteria with mean caffeine intake of 222 mg/day. The fourth study conducted by Svikis et al., (2005) found that more than one-half (57%) of a group of employed pregnant women who reported current caffeine use, met *DSM-IV* criteria for lifetime Substance Dependence as applied to caffeine.

Together, these studies found caffeine exhibited clinical features similar to those for other psychoactive drugs of abuse and that caffeine use led to problems for some individuals. Moreover, findings offer support for reviewing caffeine dependence as a clinical syndrome so that behavioral disruptions associated with its use can be addressed (Juliano et al., 2014; Strain et al., 1994).

In the recently published *DSM-5* (2013), the Substance Use Disorder workgroup determined there was insufficient evidence to include Caffeine Use Disorder in the Substance Use and Addictive Disorders chapter. In a more recent review of literature, Meredith et al., (2013) and Addicott (2014) affirmed the critical need for more epidemiological, clinical, and even genetic research on caffeine dependence, as several recent reports have shown that caffeine dependence can result in clinically significant distress and functional impairment. A review of all the caffeine dependence criteria lies beyond the scope of this thesis. However, tolerance and caffeine withdrawal, two hallmark symptoms of physical dependence, will be reviewed. Please refer to Meredith and colleagues (2013) for a more comprehensive review of the other diagnostic criteria as applied to caffeine.

Tolerance

Tolerance is defined as "an acquired change in responsiveness of an individual as a result of exposure to drug such that an increased dose of drug is necessary to produce the same degree of response, or that less effect is produced by the same dose of drug" (p. 327, Griffiths & Mumford, 1996). Chronic self-administration of caffeine can produce tolerance to many of its physiological, behavioral, and subjective effects (Hirsh, 1984; Finn & Holtzman, 1986, 1987, 1988).

In animal studies, Griffiths & Mumford (1996, 2000) and Griffiths and colleagues (2003) identified 15 laboratory studies demonstrating caffeine tolerance. Tolerance was seen at caffeine dosing frequencies ranging from once every other day (Wayner, Jolicoeur, Rondeau, & Barone, 1976) to several times daily over periods of days or weeks (Holtzman, 1983), and with doses ranging from 10mg/kg per day (Chou, Khan, Forde, & Hirsh, 1985) to 222 mg/kg per day (Ahlijanian & Takemori 1986). Tolerance was evident for a number of caffeine effects, including schedule-controlled responding, reinforcement thresholds of electrical brain stimulation, discriminative responding in caffeine-trained animals, and locomotor activity (Griffiths & Mumford, 1996).

Human studies have also reported evidence of caffeine tolerance. However, specific parameters under which tolerance can develop warrant further study (Griffiths & Mumford, 1996, 2000). For example, Evans and Griffiths (1992) found evidence using a procedure in which subjects were stratified based on caffeine preference and then chronically exposed to either caffeine (300 mg) or placebo three times a day for 18 days. During the last 14 days, participants who completed the chronic dosing regimen of caffeine did not differ significantly on mood ratings and ratings of subjective effects compared to the placebo group. Also, when 300

mg of caffeine was administered two times per day, caffeine produced significant subjective effects (tension-anxiety, jittery/nervous/shaky, and active/stimulated/energetic) in the placebo group but not in the caffeine group. This type of tolerance, which occurs after repeated administration of relatively high caffeine doses spread throughout the day for across consecutive days is called "complete tolerance," with no differentiation between caffeine effects and placebo (Griffiths & Mumford, 2000).

Several studies have demonstrated caffeine tolerance to sleep disruption (Bonnet & Arand, 1992; Hicks, Kilcourse, & Sinnott 1983; Zwyghuizen-Doorenbos, Roehrs, Lipschutz, Timms, & Roth, 1990), and there is substantial evidence that repeated caffeine administration produces decreased physiological effects of caffeine, such as diuresis, parotid gland salivation, increased metabolic rate, increased blood pressure, increased plasma norepinephrine and epinephrine, and increased plasma renin activity (Griffiths & Mumford, 2000). Several studies have shown development of complete tolerance to caffeine's effects on blood pressure and other cardiovascular and physiological responses after repeated daily dosing with caffeine (Ammon, Bieck, Mandalaz, & Verspohl, 1983; Denaro, Brown, Jacob, & Benowitz, 1991; Robertson, Wade, Workman, Woosley, & Oates, 1981).

As with many drugs, the degree of tolerance appears to vary as a function of caffeine dose, dose frequency, and number of doses received, as well as individual differences in caffeine elimination rates (Shi, Benowitz, Denaro, & Sheiner, 1993). Research also suggests that the upregulation of the A_1 receptors (i.e., increases in the number of brain adenosine receptors) by chronic caffeine exposure is what may contribute to the development of caffeine tolerance (Arnaud, 1999; Griffiths & Mumford, 1996). However, because changes have been found in a variety of other neurotransmitter receptors following chronic caffeine administration (Shi et al.,

1993), it is unclear exactly which mechanism(s) may contribute to the development of caffeine tolerance. For example, tolerance may be due to adaptive changes at the level of gene transcription (Fredholm et al., 1999) or compensatory changes in the dopaminergic system secondary to chronic adenosine receptor antagonism (Garrett, & Holtzman, 1994).

Withdrawal

Caffeine withdrawal was only recently classified as a DSM-5 diagnosis (APA, 2013). Prior to that time, there were many published reports of caffeine withdrawal (Juliano & Griffiths, 2004; Juliano et al., 2014). More recent research identified as a clinical syndrome, and researchers have been instrumental in adding caffeine withdrawal to the diagnostic nomenclature (Hasin, O'Brien, Auriacombe, Borges, Bucholz, Budney, Compton, Crowley, Ling, Petry, Schuckit, & Grant, 2013; Hughes et al., 1992c).

Withdrawal is defined as "a maladaptive behavioral change, with physiological and cognitive concomitants, that occurs when blood or tissue concentrations of a substance decline in an individual who had maintained prolonged heavy use of the substance" (p.195, APA, 2000). Withdrawal is generally thought of in context of physical dependence, and has been historically seen as a hallmark symptom of dependence. After chronic use of caffeine, abrupt cessation can produce caffeine withdrawal (Griffiths & Chausmer, 2000; Juliano, Huntley, Harrell, & Westerman, 2012).

Table 3.

Diagnostic Criteria for 292.0 Caffeine Withdrawal.

A. Prolonged daily use of caffeine.
B. Abrupt cessation of or reduction in caffeine use, followed within 24 hours by three (or more) of the following signs of symptoms:
1. Headache.
2. Marked fatigue or drowsiness.

3. Dysphoric mood, depressed mood, or irritability.
4. Difficulty concentrating.
5. Flu-like symptoms (nausea, vomiting, or muscle pain/stiffness)

C. The signs of symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The signs or symptoms are not associated with the physiological effects of another medical conditions (e.g., migraine, viral illness) and are not better explained by another mental disorder, including intoxication or withdrawal from another substance.

(APA, 2013)

The first comprehensive review of caffeine withdrawal was published in 1998c by Griffiths & Woodson. They found, in laboratory animal studies, caffeine withdrawal was demonstrated by decreases in locomotor activity (Boyd, Dolman, Knight, & Sheppard, 1965; Finn and Holtzman, 1986; Holztman, 1983; Kaplan, Greenblatt, Kent, & Cotreau-Bibbo, 1993; Nehlig & Derby, 1994), decreases in operant behavior (Carney, 1982; Carroll et al., 1989), decreases in reinforcement threshold for electrical brain stimulation (Mumford et al., 1988), an increase in the ratio of time spent in slow wave sleep stages I and II (Sinton & Petitjean, 1989), and avoidance of preferred flavor when paired with caffeine abstinence (Vitiello & Woods, 1977).

Studies of caffeine withdrawal in humans were summarized in a review by Juliano & Griffiths (2004). They found a variety of experimental procedures had been used to study caffeine withdrawal, including: "acute abstinence versus preceding caffeine baseline (not counterbalanced); acute abstinence versus caffeine; acute abstinence in caffeine consumers versus non-consumers; acute abstinence versus chronic abstinence; time-limited abstinence effects; variation in caffeine maintenance dose; acute decreases in caffeine maintenance dose; manipulation of duration of caffeine maintenance and re-administration of caffeine reverses abstinence effects (p. 11-12, Juliano & Griffiths, 2004). A detailed review of these methodological procedures lies beyond the scope of this thesis.

In the review, they summarized 42 experimental and 9 survey studies focused on validation of caffeine withdrawal. Across these studies, 13 symptoms of withdrawal were supported by strong empirical evidence. These include: headache, fatigue, decreased energy/activeness, decreased alertness, drowsiness, decreased contentedness, depressed mood, difficulty concentrating, irritability, and foggy/not clearheaded, flu-like symptoms, nausea/vomiting, and muscle pain/stiffness. Evans & Griffiths (1999) reported the "most common withdrawal symptoms include increases in headaches, drowsiness, and work difficulty (including impaired concentration) and decreases in feelings of contentment and sociability" (p. 285); however, the overall most frequently reported withdrawal symptoms is headache, which is characterized as a gradual onset, being diffuse, throbbing, and at times severe (APA, 2013; Griffiths & Woodson, 1988c). Further, by the end of the first day of abstinence approximately 50% of regular caffeine users reported headache (Juliano et al., 2014).

Several other behavioral, cognitive, and psychomotor withdrawal symptoms have been described, as well as subjective reports of physical ailments such as: fatigue/lethargy, and muscle pain, dysphoric feelings of anxiety, blurred vision, decreased alertness, jitteriness, irritability, increased reporting of stress, changes in quantitative electroencephalography (EEG), decreased blood pressure, tremors, and upset stomach (Arnaud, 1999; Griffiths & Mumford 1996, 2000, 2006; Griffiths & Woodson, 1988c; Griffiths et al., 2003; Griffiths, Evans, Heishman, Preston, Sannerud, Wolf, & Woodson; 1990; Jones, Herning, Cadet, & Griffiths, 2000; Juliano & Griffiths, 2004; Rizzo, Stamps, & Fehr, 1988; Silverman, Evans, Strain, & Griffiths, 1992; Strain et al. 1994; Schuh & Griffiths, 1997; Weinberg & Bealer, 2001). Furthermore, large doses of caffeine (above 250 mg) have been found to act as a diuretic, which may potentially result in a fluid imbalance (Maughan & Griffin, 2003).

The inclusion of Caffeine Withdrawal in the *DSM-5* (2013) as a substance-related disorder has brought more attention to the recognition clinical relevance and significance (Hughes et al., 1992c; APA, 2013). The criteria for the disorder of caffeine withdrawal are summarized in Table 3 described by the APA (2013). What follows is a review of the animal and human research studies that contributed to this decision.

Caffeine-Related Withdrawal Symptoms

Headache

Headaches are the hallmark symptoms of caffeine withdrawal and have been the focus of much research (Juliano et al., 2014). In their review, Juliano & Griffiths 2004 found that headache was the most frequently assessed and reported symptom, with 48 experimental studies and 6 survey studies providing evidence. The average percentage of caffeine consumers reporting headache across the 19 experimental studies was 47%, with a range from 9% to 100% (Juliano & Griffiths, 2004). Among experimental studies assessing the severity of reported caffeine withdrawal headache, moderate to several headaches were reported 50% of consumers in the experimental studies, and 24% of caffeine consumers in the survey studies (Juliano & Griffiths, 2004).

In regards to the different methodologies used to draw inferences about the prevalence of headaches as a caffeine withdrawal symptom, Juliano & Griffiths (2004) reported headaches have been demonstrated in various studies comparing acute caffeine abstinence versus a preceding baseline condition (Couturier Laman, van Duijn, & van Duijn, 1997; Edelstein, Keaton-Braster, & Burg, 1983; Griffiths et al., 1986a; Höfer & Bättig 1994a; Höfer & Bättig 1994b; Lader, Cardwell, Shine, & Scott, 1996; Naismith, Akinyanju, Szanto, & Yudkin, 1970; Roller, 1981; Silverman et al., 1992), and versus a caffeine consumption condition (Brauer,

Buican, & de Wit, 1994; Bruce, Scott, Shine, & Lader, 1991; Driesbach & Pfeiffer, 1943; Evans & Griffiths, 1999; Comer, Haney, Foltin, & Fischman, 1997; Evans & Griffiths, 1992; Goldstein, 1964; Goldstein, Kaizer, & Whitby, 1969; Griffiths et al., 1990; Hughes et al., 1992a; Hughes, Hunt, Higgins, Bickel, Fenwick, & Pepper 1991; Hughes et al., 1995; James, 1998; Lane, 1994; Lane, 1997; Lane & Phillips-Bute, 1998; Liguori, et al., 1997b; Mitchell, de Wit, & Zacny, 1995; Oliveto et al., 1992a, Oliveto, et al., 1992b; Schuh & Griffiths, 1998; Silverman et al., 1992; Strain et al., 1994; Duseldor & Katan, 1990; Van Soeren & Graham, 1998).

Signs and symptoms of caffeine withdrawal headache were also compared during acute caffeine abstinence and chronic caffeine abstinence conditions (Griffiths et al., 1990; Bruce et al., 1991; James, 1998; Tinley, Yeomans, & Durlach, 2003) as well as acute caffeine abstinence in caffeine consumers with non-consumers (Richardson, Rogers, Elliman, & O'Dell, 1995). Juliano & Griffiths (2004) also reported that several "studies have also shown that abstinence induced headache is time-limited and is rapidly (usually within 30–60 min) and often completely reversed after re-administration of caffeine (Driesbach & Pfeiffer 1943; Goldstein et al. 1969; Roller 1981; Couturier et al. 1997; Tinley et al. 2003), with the magnitude of reversal being an increasing function of the re-administered caffeine dose (Goldstein et al. 1969)" (p. 12).

Caffeine withdrawal headache has been described as having a gradual onset (Driesbach & Pfeiffer 1943; Greden, Victor, Fontaine, & Lubetsky, 1980; Roller 1981; Griffiths et al. 1990), severe (Griffiths & Woodson 1988), diffuse (Driesbach & Pfeiffer 1943; Greden 1974; Greden et al. 1980; Lader et al. 1996), and throbbing (Driesbach and Pfeiffer 1943; Greden 1974; Greden et al. 1980; Lader et al. 1996), but are distinct from migraine headaches (Driesbach & Pfeiffer 1943) (Juliano & Griffiths, 2004). Also, important to note is that the incidence of caffeine withdrawal headache does not necessarily correlate with the occurrence of other symptoms (e.g.,

fatigue), which suggests that other signs and symptoms of caffeine withdrawal are not merely a result of headache (Griffiths et al., 1990; Griffiths & Woodson, 1988). Research has demonstrated that caffeine abstinence produces rebound cerebral vasodilatation and increased cerebral blood flow, which has been speculated as the primary mechanism contributing to caffeine withdrawal headache (Jones et al., 2000; Sigmon, Herning, Better, Cadet, & Griffiths, 2009).

Marked fatigue or drowsiness

Marked fatigue and drowsiness were combined to form a single criterion. *Marked fatigue* or tiredness is defined by feelings of laziness; being sluggish, lethargic, sleepy, or worn out. In contrast, *drowsiness* is characterized by feelings of sleepiness, sedation, or decreased wakefulness. Fatigue was demonstrated in 32 of 38 studies (84%), with 27% o caffeine consumers in experimental reporting fatigue. Drowsiness was reported in 21 of 27 experimental studies (78%), with approximately 45% of consumers reporting the symptom.

Several methodological approaches have also been used to demonstrate the occurrence of marked fatigue and drowsiness. For example, signs and symptoms of fatigue were demonstrated in studies comparing acute caffeine abstinence with a preceding baseline condition (Griffiths et al, 1986; Lader et al., 1996; Naismith et al., 1970; Roller, 198; Silverman et al., 1992), as was drowsiness (Griffiths et al., 1986; Höfer & Bättig 1994a; Höfer & Bättig 1994b; Lader et al., 1996; Silverman et al., 1992). Both fatigue (Bruce et al., 1991; Comer et al., 1997; Driesbach & Pfeiffer, 1943; Evans & Griffiths, 1999; Garrett and Griffiths, 1998; Goldstein et al., 1969; Griffiths et al., 1990; Hale et al., 1995; Hughes et al., 1992a; Hughes et al., 1991; Hughes et al., 1995; Lane, 1994; Lane, 1997; Lane and Phillips-Bute, 1998; Liguori et al., 1997; Liguori & Hughes, 1997; Mitchell et al., 1995; Oliveto et al., 1992a; Oliveto et al., 1992b; Phillips-Bute &

Lane, 1998; Richardson et al., 1995; Rodgers, Richardson, Elliman, 1995; Schuh & Griffiths, 1997; Silverman et al., 1992; Strain et al., 1994; Streufer, Pogash, Miller, Gingrich, Landis, Lonardi, Severs, & Roache, 1995; Van Soeren & Graham, 1998) and drowsiness (Bruce et al., 1991; Comer et al., 1997, Hale et al., 1995; Hughes et al., 1995; Hughes et al., 1992a; Hughes et al., 1991; Goldstein et al., 1969; Griffiths et al., 1990; Lane, 1994; Lane, 1997; Lane & Phillips-Bute, 1998; Liguori & Hughes, 1997; Liguori et al., 1997; Oliveto et al., 1992a; Oliveto et al., 1992b; Phillips-Bute & Lane, 1998; Richardson, et al., 1995; Silverman et al., 1992; Streufert et al., 1995) have been demonstrated in studies comparing acute caffeine abstinence versus caffeine consumption conditions (Juliano & Griffiths, 2004).

Only Richardson and colleagues (1995) demonstrated caffeine withdrawal fatigue after comparing acute caffeine abstinence in caffeine consumers versus non-consumers, but both Goldstein et al., (1969) and Richardson et al., (1995) demonstrated caffeine withdrawal drowsiness using the same methodological procedures. When acute abstinence was compared with chronic abstinence, caffeine withdrawal fatigue was demonstrated in 4 studies (Bruce et al., 1991; Garrett and Griffiths, 1998; Griffiths et al., 1990; Richardson et al., 1995) and drowsiness in 3 studies (Garrett & Griffiths, 1998; Griffiths et al., 1990; Richardson et al., 1995). Similar to what was found for caffeine withdrawal headache, several studies shown that abstinence-induced fatigue and drowsiness are time limited (Griffiths et al., 1986; Griffiths et al., 1990; Höfer & Bättig 1994a; Lader et al., 1996; Naismith et al., 1970; Richardson et al., 1995). Further, caffeine withdrawal fatigue (Roller 1981) and drowsiness (Goldstein et al. 1969) are completely reversed after re-administration of caffeine; however, caffeine withdrawal drowsiness is more rapidly reversed (30-60min.). In addition, severity of both fatigued and drowsiness symptoms are positively correlated with daily caffeine dose before abstinence (Rogers et al.1995;

Silverman et al. 1992) (Juliano & Griffiths, 2004).

Dysphoric Mood, Depressed Mood, or Irritability

This symptom of caffeine withdrawal is present when the individual presents with depressed or dysphoric mood (feelings of sadness or dejection) and/or irritability (feeling angry, cross or grumpy. Juliano & Griffiths (2004), in their review, found depressed mood reported in 9 of 29 experimental studies (31%) and irritability in 8 of 23 experimental studies (35%). The average percentage of consumers reporting depressed mood across experimental studies was 16% (range 11-36%) and in 2 survey studies, 4% (Hughes et al., 1998) and 9% (Oberstar, Berstein, & Thuras, 2002). The average percentage reporting irritability was 29% in one experimental study (Griffiths et al., 1990) and 9% in another (Hughes et al., 1995) with 21% (Goldstein & Kaizer, 1969) and 20% (Hughes et al., 1998) being reported in 2 survey studies.

Depressed mood and irritability were found in numerous studies using various methodological approaches, such as, comparing acute caffeine abstinence to a baseline condition (Silverman et al., 1992), and to active caffeine consumption (depressed mood: Griffiths et al., 1990; Hale et al., 1995; Hughes et al., 1995; Lane & Phillips-Bute, 1998; Richardson et al., 1995; Silverman et al., 1992; Strain et al., 1994; irritability: Goldstein et al., 1969; Griffiths et al., 1990; Lane & Phillips-Bute, 1998; Liguori et al., 1997b; Silverman et al., 1992; Streufer et al., 1995). Depressed mood (Garret & Griffiths 1998; Griffiths et al., 1990; Richardson et al., 1995) and irritability (Garret & Griffiths, 1998; Griffiths et al., 1990) were also evident in comparisons of acute and chronic caffeine abstinence conditions, and in comparing acute caffeine abstinence in caffeine consumers and non-consumers (Goldstein et al., 1969; Richardson et al., 1995). Only one study found abstinence-induced depressed mood and irritability were time limited (Griffiths et al., 1990), and only Goldstein et al., (1969) found

caffeine withdrawal irritability to be completely reversed after re-administration of caffeine. Similar to other caffeine withdrawal symptoms, the degree of reversal is an increasing function of the re-administered caffeine dosage (Goldstein et al. 1969) (Juliano & Griffiths, 2004).

Difficulty Concentrating

Difficulty concentrating or decreased ability to concentrate was associated with caffeine withdrawal in 8 of 12 experimental studies (67%) with over three-fourths (79%) of participants in one study reporting trouble concentrating (Griffiths et al., 1990). In contrast, only 11% of participants in one survey study reported trouble concentrating (Juliano & Griffiths, 2004). The methodological approaches included comparing the signs and symptoms of difficulty concentrating during acute caffeine abstinence versus baseline (Lader et al., 1996) to a caffeine administration condition (Garrett & Griffiths, 1998; Griffiths et al., 1990; Jones et al., 2000; Lane, 1997; Lane & Phillips-Bute, 199; Streufert et al., 1995) and versus chronic caffeine abstinence conditions (Garrett & Griffiths, 1998; Griffiths et al., 1990). Griffiths and colleagues (1990) found that abstinence-induced difficulty concentrating is time limited and that symptom severity is positively correlated with daily caffeine dose prior to abstinence (Lane, 1997) (Juliano & Griffiths, 2004).

Flu-like Symptoms (nausea, vomiting, or muscle pain/stiffness)

Flu-like symptoms (feeling sick, queasy or dizzy; perspiring) were reported in 9 of 17 (53%) experimental studies of caffeine withdrawal with an incidence rate of 31% (Lane, 1997). Flu-like symptoms were seen in studies comparing acute caffeine abstinence with a preceding baseline condition (Silverman et al., 1992), a caffeine administration condition (Griffiths et al., 19990; Evans & Griffiths, 1999; Lane, 1997; Schuh & Griffiths, 1998; Silverman et al., 1992; Van Soeren & Graham, 1998), and a chronic caffeine abstinence condition (Griffiths et al.,

1990). Only one study has shown that abstinence-induced flu-like symptoms are time-limited (Griffiths et al., 1990); however, as of 2004 no study has been able to demonstrate an incidence of these symptoms after comparing acute caffeine abstinence in consumers versus non-consumers (Juliano & Griffiths, 2004).

Consistent with other caffeine withdrawal symptoms, the severity of flu-like symptoms is also an increasing function of caffeine maintenance dose prior to abstinence (Lane and Phillips-Bute 1998; Evans and Griffiths 1999). Juliano & Griffiths (2004) found that because most of the experimental studies demonstrating empirically supported increases in flu-like symptoms involved comparisons of caffeine abstinence to a caffeine administration condition, the category of these symptoms as a single symptom failed to meet Juliano & Griffiths (2004) validity criteria. However, Juliano & Griffiths (2004) report that, "the category appears to reflect a genuine withdrawal effect because endorsement of flu-like symptoms is time limited (Griffiths et al. 1990) and it is implausible that such placebo versus caffeine differences represent a direct effect of caffeine in suppressing naturally occurring flu-like symptoms" (p. 13). Given this incidence of data, Juliano & Griffiths (2004) believe the category appears to be a valid caffeine withdrawal effect, and based on factor analysis studies, the DSM-5 Work Group included flu-like symptoms as part of the diagnosis (APA, 2013; Hasin et al., 2013).

Nausea/vomiting (feeling nauseated or having an upset stomach, or vomiting) can be characteristic of flu-like symptoms, and has been demonstrated in 6 of 24 experimental studies (25%), and across experimental studies demonstrating these symptoms, the median percentage of individuals reporting nausea/vomiting was 21% (range 10–33%). Two survey studies found the percentage of subjects reporting nausea/vomiting during caffeine abstinence was 3% (Hughes et al., 1998) and 21% (Bernstein, Carroll, Thuras, Cosgrove, & Roth, 2002). These symptoms have

only been demonstrated in studies comparing acute caffeine abstinence with a caffeine administration condition (Driesbach & Pfeiffer; Höfer & Bättig 1994a; Liguori & Hughes, 1997; Liguori et al., 1997b; Swederlow, Eastvold, Gerbranda, Uyan, Hartman, Doan, & Auerbach, 2000). However, instances of caffeine withdrawal induced nausea/vomiting have been reported in experimental studies (Griffiths et al. 1990; Silverman et al. 1992; Strain et al. 1994) and survey studies (Hughes et al. 1998; Oberstar et al. 2002), in addition to, case reports (Cacciatore, Helbling, Jost, & Hess, 1996; Rainey, 1985). Nausea/vomiting also failed to meet Juliano & Griffiths (2004) validity criteria; however, they judged these symptoms to be valid criteria for caffeine withdrawal syndrome, and the DSM-5 Work Group also decided to include these symptoms given their factor analysis studies (APA, 2013; Hasin et al., 2013).

The cluster of symptoms identified as muscle pain/stiffness, which can also be characteristic of flu-like symptoms, has been demonstrated in 4 of 15 experimental studies (27%), with one study reporting an incidence of muscle pain/stiffness as high as 43% (Griffiths et al., 1990). These symptoms have been demonstrated in studies comparing acute caffeine abstinence with a preceding baseline condition (Höfer & Bättig 1994b; Roller, 1981). Griffiths and colleagues (1990) demonstrated muscle pain/stiffness after comparing acute caffeine abstinence versus a caffeine administration condition and a chronic caffeine abstinence condition, in addition to providing evidence showing that abstinence-induced muscle pain/stiffness is time limited.

Additionally, muscle pain/stiffness has also been described in case reports (Cobbs 1982; Stringer & Watson 1987), including one report where a musculoskeletal examination was administered during caffeine abstinence (Reeves, Struve, & Patrick, 1997). These symptoms also failed to meet the validity criteria set forth by Juliano & Griffiths (2004); however

consistent with other symptoms associated with caffeine withdrawal flu-like signs, Juliano & Griffiths (2004) believe that "muscle pain/stiffness represents a true withdrawal symptom unconfounded by the direct effects of caffeine seems reasonable because it is improbable that caffeine suppresses naturally occurring muscle pain/ stiffness" (p. 16). Ultimately, the DSM-5 Work Group also chose to include this symptom in the diagnosis given the results of their factor analysis studies (APA, 2013; Hasin et al., 20130).

Characteristics of Caffeine Withdrawal Syndrome

Functional Impairment & Prevalence

In regards to Criterion C of caffeine withdrawal, the aforementioned symptoms represent clinical importance given that they may induce significant distress or impairment in daily functioning (Evans & Griffiths, 1998; Juliano et al., 2014). This has been demonstrated in the literature indicating that for caffeine users who abruptly abstain, caffeine withdrawal signs and symptoms may occur at clinically significant levels in about 10 to 50% of caffeine consumers (APA, 2013; Griffiths & Mumford, 1996; Juliano & Griffiths, 2004; Juliano et al., 2014).

Functional impairment has been described in the literature as being unable to care for children, or inability to go to work, school, or church (Strain et al., 1994). In recent years, there have been several reports of caffeine withdrawal incidences. Aside from information pertaining to caffeine dependence, Hughes et al., (1992a) found 42% of their current caffeine users also reported withdrawal headaches, fatigue or drowsiness when they abstained from caffeine after 24 hours.

Additionally, Silverman and colleagues (1992) investigated 62 individuals from the general community and administered caffeine in doses similar to that of the general population in the United States at that time (mean 235 mg/day). Under 48-hr, double-blind caffeine abstinence

trials the investigators found that during caffeine withdrawal, 52% reported moderate or severe headache, and 8-11% reported abnormally high scores on standardized depression, anxiety, and fatigue scales. Also, in 1999, Dews, Curtis, Hanford, and O'Brien surveyed 1,112 individuals and found that 61% reported daily caffeine consumption, and among those consumers, 11% reported symptoms of caffeine withdrawal after stopping caffeine. Overall, it has been reported that more than 70% of individuals experience at least one caffeine withdrawal symptom after attempting to permanently discontinue their caffeine use (APA, 2013).

Dosing Parameters and Time Course of Withdrawal

Cessation of caffeine intake among habitual users may induce symptoms of caffeine withdrawal among those who regularly consume low to moderate amounts of caffeine (20-200 mg) and in doses as low as 100 m/day, which is the equivalent of about one cup of coffee or two cans of cola, or doses as high as 900 mg/day (Bruce, Scott, Shine, & Lader, 1991; Evans & Griffiths, 1999; Griffiths et al., 1990; Nehlig, 1999; Weinberg & Bealer, 2001). There is sound clinical evidence that the incidence and/or severity of caffeine withdrawal are positively correlated with increases in chronic daily caffeine maintenance dose. In 1999, Evans & Griffith established a parametric range describing the effect of caffeine withdrawal as a function of caffeine dosing conditions. The authors demonstrated the severity of caffeine withdrawal symptoms of headache and poor mood was substantially higher after abstinence from 600mg of caffeine compared to 100mg/day. Additionally, the authors concluded that the higher the substitution doses of caffeine administered compared to the usual maintenance dose (25, 50, 100, 200, or 300 mg), the less severe the withdrawal symptoms (Evans & Griffiths, 1999).

Caffeine withdrawal symptoms follows an orderly time course, meaning it can begin within 12 to 24 hours after caffeine cessation, peak at 20 to 51 hours, and last approximately one

week (Griffiths & Chausmer, 2000; Griffiths & Mumford, 2000; Juliano & Griffiths, 2004; Juliano et al., 2014). Research has also demonstrated that the duration of caffeine withdrawal ranges from 2-9 days (Juliano & Griffiths, 2004). However, it has been reported that a gradual reduction in caffeine consumption over a period of days or weeks may reduce the severity and incidence of caffeine withdrawal symptoms (APA, 2013). For example, re-administration of low doses of caffeine is sufficient to suppress significant caffeine withdrawal headache (Juliano et al., 2014).

Caffeine Withdrawal and Habitual Caffeine Consumption

Among regular caffeine consumers, the avoidance of caffeine withdrawal symptoms plays a critical role in the reinforcing effects of caffeine (Juliano et al., 2014; Schuh & Griffiths, 1997). For example, an experimental study conducted by Hughes and colleagues (1993) showed participants who reported caffeine withdrawal symptoms after consuming decaffeinated coffee were found twice as likely to choose caffeinated coffee over decaf during a choice test. Additionally, Griffiths et al., (1986a) and Garrett & Griffiths (1989) experimentally manipulated caffeine physical dependence and demonstrated that participants choose caffeine more than twice as often while physically dependent compared to when not physically dependent. Furthermore, a retrospective questionnaire study conducted by Goldstein & Kaizer (1969) and multiple double-blind experimental studies (Garrett & Griffiths 1998; Griffiths et al. 1986; Hughes et al. 1993; Liguori & Hughes 1997; Schuh & Griffiths, 1997) aimed at assessing behavioral measure of caffeine reinforcement found that the avoidance of caffeine withdrawal symptoms is directly related to habitual caffeine consumption. Furthermore, several studies have demonstrated the relationship between abstinence-associated caffeine withdrawal and beverage flavor preferences (Rogers et al. 1995; Tinley et al. 2003; Yeomans et al. 1998, 2000, 2001, 2002) (Juliano &

Griffiths, 2004).

Biological Basis of Caffeine Withdrawal

Research has suggested that the pharmacological and physiological mechanism underlying caffeine physical dependence and withdrawal is also related to the endogenous neuromodulator adenosine, similarly as it is related to caffeine tolerance (Griffiths & Mumford, 1996). Given that caffeine is a competitive antagonist of adenosine (Juliano et al., 2014), chronic caffeine administration has been reported to increase brain adenosine receptors (Daly, 1993; Daly & Fredholm, 1998), to shift brain A_1 adenosine receptors to a high affinity state (Green & Stiles, 1986), and to increase functional sensitivity to adenosine (Ahlijanian & Takemori, 1986; Biaggioni, Paul, Puckett, & Arzubiaga, 199; Green & Stiles, 1986; von Borstel, Wurtman, & Conlay, 1983). This increase in functional sensitivity to endogenous adenosine has also been proposed as the underlying mechanism associated with caffeine withdrawal headache and fatigue (Hirsh, 1984; von Borstel et al., 1983); although, research on these mechanisms regarding dependence and withdrawal need to be expanded considerably (Griffiths & Mumford, 1996).

Individual Differences in Caffeine Use & Withdrawal

Considerable within and between subject variability has been found in the occurrence caffeine withdrawal. Studies to-date suggest that in addition to chronic use of caffeine, the likelihood of experiencing caffeine withdrawal may differ by gender, personality traits, and other substance use histories, including cigarette smoking (Juliano & Griffiths, 2004). Genetic polymorphisms may also play a role (e.g., A_1 and A_{2A} adenosine receptor gene).

Gender

For many substance use disorders, the etiology, course, and treatment varies considerably

by gender. Overall, substance use disorders are more prevalent in men than women (SAMHSA, 2016). Females, however, show accelerated progression from first use of a substance to onset of dependence and admission to treatment. (i.e., telescoping) (Greenfield et al., 2010). Furthermore, research on sex differences from the field of addiction found that among daily users, females were more sensitive than men to subjective effects of marijuana (Cooper & Haney, 2014) and that women with lifetime cannabis use disorder were more likely to develop a psychiatric disorder (Khan et al., 2013; Zilberman, Tavares, Blume, & el-Guebaly, 2002). Research has also suggested that nicotine metabolism is faster in women than men (Benowitz et al., 2006) and faster nicotine metabolizers have poorer smoking cessation outcomes from nicotine replacement therapy (e.g., nicotine patch) (Lerman et al., 2006). Additionally, research has suggested that among prescription opioid users, the rates of psychological distress are significantly higher among women than men, and that there were significant gender differences associated with the likelihood of developing prescription opioid abuse or dependence (Back, Payne, Simpson, & Brady, 2010).

With regard to caffeine, Temple and colleagues (2009) reported that adolescent males may be more susceptible to the reinforcing properties of caffeine than adolescent females. Research has also found that physiological responses to caffeine are moderated by gender and chronic caffeine consumption (Temple et al., 2010; Temple & Ziegler, 2011). For example, Adan and colleagues (2008), found among undergraduate students, lower doses of caffeine induced greater physiological effects in men than in women, whereas decaffeinated beverages produced greater effects in women compared to men.

Gender differences in amounts of caffeine consumption have been reported, but findings are mixed. A population-level study conducted by Mitchell and colleagues (2014) found that

among adult (≥ 18 years) caffeine users, men consumed more total caffeine from beverages than adult women; however, when the investigators adjusted for body weight (i.e., mg/kg/day), they found that women consumed slightly more for all combined caffeinated beverages (e.g., coffee, tea, caffeinated carbonated soft drinks, chocolate drinks, energy drinks, and energy shots). No gender differences were found among those who consumed only carbonated soft drinks or energy drinks (Mitchell et al., 2014). This is in contrast to a study conducted of active duty military personnel (18+ years) where women consumed less caffeine than men after adjusting for body weight (Lieberman et al., 2012). Moreover, a study conducted by Demura, Aoki, Mizusawa, Soukura, Noda, & Sato (2013) found that among 1189 young people (567 males aged 19.3 ± 1.5 years; 622 females aged 19.1 ± 1.2 years), coffee consumption rates were significantly higher in males (50.8%) than in females (32.8%). Also, and as mentioned above, Drewnowski & Rehm (2016) and Fulgoni and colleagues (2015) both found mean caffeine intake to be higher in men than in women. Additionally, in a sample of U.S. college students Landrum (1992) found females reported lower weekly caffeine consumption than males (713.72 mg vs. 822.20 mg, respectively).

Kendler, Myers, & Gardner (2006), in a population-based twin study, found that after controlling for age, mean daily caffeine consumption was greater in males than in females, with heavy caffeine use also more common in men (17.3%) than in women (11.4%). The frequency of caffeine toxicity did not differ by gender; however, with mean number of caffeine dependence symptoms was significantly greater in males than in females. Furthermore, 47.8% of men versus 36.6% of women reported one or more symptoms of caffeine dependence.

While the above findings found men consume more caffeine than women, others found the opposite pattern. Jacobson & Bouher, (1991) for example, found in the general population,

females consumed more caffeine than males (393.4mg and 349.1mg per day, respectively). Moreover, in another study conducted by Frary et al., (2005), adult men had higher caffeine intakes compared to women, also after adjusting for weight; although, this was not found among 18- to 24-year-olds where only little differences were observed (1.2 vs. 1.1 mg/kg/day). In addition, a study of caffeine intake among U.S. adults using the 2007-2012 NAHNES data found that caffeine consumption was not significantly associated with gender (Lieberman, Agarwal, & Fulgoni, 2016).

As mentioned previously, energy drink consumption has gained popularity since the 1997 debut of Red Bull. A study conducted by Malinauskas and colleagues (2007) found that female college students reported higher rates of energy drink consumption than males, but a study conducted by Attila & Çakir (2011) found that men were 1.5 times more likely than women to use energy drinks. Also, according the Drug Abuse Warning Network (DAWN) report, since 2007 more emergency department visits involving energy drinks were made by males when compared to females, and visits by both genders have doubled from 2007 to 2011 (SAMHSA, 2013).

Many reasons for why gender differences exist within substance abusers have been hypothesized. For example, it is suggested that ovarian hormones (e.g., estrogen) can contribute to the gender differences observed in humans and animals, along with pharmacokinetics in hepatic metabolism, and other biological vulnerabilities, such as gender differences in body fat, water proportions, and differences in gastric enzymatic activity. In regards to caffeine, females metabolize caffeine 20% to 30% faster than males (Franconi, Brunelleschi, Steardo, & Cuomo, 2007; Nawrot, et al., 2003); however, women who use oral contraceptives have approximately double the caffeine half-life compared to those who do not use them (Patwardhan, Desmond,

Johnson, & Schenker, 1980). Additionally, Temple & Ziegler (2011), found gender differences in cardiovascular responses to caffeine, suggesting that these differences may be related to steroid hormone concentrations.

The role of sex/gender differences in outcomes from the field of drug addiction is becoming an important topic among National Institute of Health-funded research (Clayton & Collins, 2014). There has been a growing recognition and concern that animal model research is largely male only, and that human research lacks gender/sex analyses. Therefore, the NIH expects that sex as a biological variable will be factored into research designs, analyses, and reporting in vertebrate animal and human studies (Clayton & Collins, 2014). Overall, reasons for gender differences in drug abuse are not yet clear and further research regarding pharmacodynamics, pharmacodynamics, and psychosocial factors is warranted (Greenfield, Back, Lawson, & Brady, 2010; Roth et al., 2004; Zilberman, Tavares, el-Guebaly, 2003) and analyzing data by sex/gender at all levels of analysis in both animal and human studies will lead to better outcomes and potentially fill in knowledge gaps.

Co-morbid Alcohol & Nicotine Use

Heavy caffeine use has been observed among individuals who abuse alcohol or meet diagnosis for clinical dependence on alcohol, which may increase their risk for caffeine withdrawal after acute caffeine cessation (APA, 2013; Hughes et al., 1993; Istvan & Matarazzo, 1984; Swanson, Lee, & Hopp, 1994; Kozlowski, Henningfield, Keenan, Lei, Leigh, Jelinek, Pope, & Haertzen, 1993). One study examining individuals fulfilling a generic *DSM-IV* (1994) substance dependence diagnostic criteria for caffeine found that approximately 60% had a past diagnosis of alcohol abuse or dependence (Strain et al., 1994). Among the general population, it is common belief that caffeine reverses the impairing effects of alcohol; however, research

investigating such effects is largely incomplete and demonstrates discrepancies across various subjective and behavioral measures (Aubin, Laureaux, Tilikete, & Barrucand, 1999; Juliano et al., 2009). It has also been demonstrated that long-term alcohol use slows caffeine elimination rate (Benowitz, 1990, James, 1991).

Moreover, it has been demonstrated that caffeine intake is strongly associated with cigarette smoking (Brice & Smith, 2002; Gurpegui, Jurado, Luna, Fernádez-Molina, Moreno-Abril, & Gálvez, 2007; Lieberman et al., 2016) such that cigarette smokers consume more caffeine than nonsmokers (Swanson et al., 1994). Research applying an event time-series analysis suggested that cigarette smoking and coffee drinking conditionally covary (Emurian, Nellis, Brady, & Ray, 1982). Studies also suggest that smoking decreases caffeine's half-life by 30 to 50% (Hart, Farrell, Cooksley, & Powell, 1976; Joeres, Klinker, Heusler, Epping, Zilly, & Richter, 1988; Murphy, Mcivor, Yap, Cooksley, Halliday, & Powell, 1988).

Preclinical (Gasior, Jaszuna, Munzar, Witkin, & Goldberg, 2002; Liu & Jernigan, 2012; Shoaib, Swanner, Yasar, & Goldberg, 1999) and clinical investigations (Jones & Griffiths, 2003) have also demonstrated caffeine's ability to increase the discriminative stimulus effects and reinforcing effects of intravenous nicotine (Juliano et al., 2014; Tanda & Goldberg, 2000). However, research has failed to reliably show caffeine's ability to alter the effects of nicotine or increase cigarette/nicotine self-administration (Blank, Kleykamp, Jennings, & Eissenbert, 2007; Chait & Griffiths, 1983; 253-255; Perkins, Fonte, Stolinski, Blakesley-ball, & Wilson, 2005). The pharmacologic effects of caffeine have been hypothesized to influence this coffee-smoking interaction; however, the above research suggests other factors also effect this interaction (Juliano et al., 2014).

One study has demonstrated that caffeine can increase the analgesic effects of cigarette

smoking (Nastase, Ioan, Braga, Zagrean, & Moldovan, 2007) and several studies (Benowitz, Hall, & Modin, 1989; Brown, Jacob, Wilson, & Benowitz, 1988) have shown that "cigarette smoking abstinence can produce substantial increases in caffeine blood levels among heavy caffeine consumers, presumable because of the reversal of cigarette smoking-induced caffeine metabolism" (p.193, Juliano et al., 2014). Environmental factors also contribute to the correlation between cigarette smoking and caffeine use, as suggested by twin and co-occurrence studies (Hetterman, Corey, & Kendler, 1999; Kozlowski et al., 1993; Swan, Carmelli, & Cardon, 1996; Swan, Carmelli, Cardon, 1997).

Furthermore, Kozlowski and colleagues (1993) also suggested that caffeine, alcohol, and nicotine disorders cluster together, while Strain et al., (1994) found that caffeine dependence is concurrent with past substance use disorders, namely alcohol abuse/dependence.

Personality

One area of research directed at advancing the knowledge of interindividual differences and susceptibility to drug reinforcement and substance abuse has focused on personality traits. Several personality factors, such as anxiety proneness, depression-proneness, impulsivity, and sensation seeking, have all been shown to be associated with risk for substance use patterns and disorders (Jones & Lejuez, 2005; Woicik, Stewart, Pihl, & Conrod, 2009). Specifically, reactions to caffeine have been found to depend on certain personality types, particularly extroversion versus introversion (Primavera, Simon, & Camisa, 1975; Revelle, Humphreys, Simon, & Gilliand, 1980; Smith, Wilson, & Jones, 1983), which has similarly been found among those who abuse cocaine and alcohol (Johnson, Tobin, & Cellucci, 1992; Richards, Zhang, Mitchell, & DeWit, 1999). As defined by Smith (2012) extroversion "reflects the degree to which a person is outgoing and interactive with other people" and…seek excitement and social

activity in an effort to heighten their arousal level, whereas introverts tend to avoid social situations in an effort to keep such arousal to a minimum" (p. 71).

In 1992, Landrum administered the Caffeine Consumption Questionnaire (CCQ) and various personality measures to 57 female and 59 male college students and found that high caffeine consumers were significantly positively correlated with extraversion as described by Eysenck. Furthermore, research conducted by Smillie and Gokcen (2010) has demonstrated interactions between caffeine use (200 mg), extraversion, and working memory tasks, where caffeine was found to provide a greater benefit to those who are extraverted. In 2012, Smith found similar results. Even though findings suggest associations between personality traits and caffeine consumption, some studies provided little evidence to suggest personality traits are connected with caffeine consumption (Brice & Smith, 2002; Hewlett & Smith, 2006; Liguori, Grass, & Hughes, 1999; Primavera, Simon, & Camisa, 1975), and very little research has focused on caffeine dependence (Jones & Lejuez, 2005), which emphasizes the necessity for future research focused on understanding the psychological characteristics of caffeine consumers.

Anxiety, Depression & Family History

Other psychological characteristics have also been related to caffeine use (Kendler, Myers, & Gardner, 2006), such as anxiety and depression (Broderick & Benjamin, 2004; Gilliland & Andress, 1981; James & Crosbie, 1987; Richards & Smith, 2015). A study conducted by Juliano et al., (2012) examining individuals seeking treatment for problematic caffeine use found that anxiety and mood disorders were the most prevalent co-occurring diagnoses (17% each), and 26% of individuals reported a lifetime diagnoses of anxiety while 42% reported a lifetime diagnoses of mood disorders.

Caffeine's anxiogenic properties have been recognized for quite some time (Juliano et al., 2009), and individuals diagnosed with anxiety disorders appear to be especially sensitive to the subjective and physiological effects of caffeine, in addition to reporting greater symptoms of anxiety arousal after consuming caffeine versus control subjects (Beck & Berisford, 1992; Bruce, Scott, Shine, & Lader, 1992; Boulenger, Uhde, Wolff, & Post, 1984; Charney, Heninger, & Jatlow, 1985; Lee, Cameron, & Greden 1985; Lee, Flegel, Greden, & Caeron, 1988; Masdrakis, Papakostas, Vaidakis, Papageorgiou, & Phlivanidis, 2008; Trapp, Allen, O'Sullivan, Robinson, Jacoby, & Oddy, 2013). Caffeine use has also been associated with increased scores on the Beck Anxiety Inventory (Dosh, Helmbrecht, Anestis, Guenthner, Kelly, & Martin, 2010). Additionally, it has been posited that persons with anxiety disorders tend to find the stimulus effects of caffeine as aversive, and several studies have demonstrated those with anxiety disorders, particularly panic disorders, report lower levels of caffeine intake when compared to healthy controls (Juliano et al., 2009; Lee et al., 1985; Lee et al., 1988; Rihs, Muller, & Baumann, 1996; Uhde, 1990); however, some studies have failed to replicate this association of greater anxiety levels and caffeine use (Charney et al., 1985; Hewlett & Smith, 2006; Holle, Heimberg, Sweet, & Holt, 1995). Therefore, as Juliano and colleagues (2009) state, "it seems reasonable to conclude that some but not all individuals with high anxiety levels will naturally avoid caffeine" (p. 169). Moreover, it has been demonstrated that individuals with A1 and A_{2a} adenosine receptor gene polymorphisms are at greater risk of caffeine-induced anxiety (Alsene, Deckert, Sand, & de Wit, 2003).

Another variable that influences caffeine consumption is depressed mood. Kendler, Myers, & O'Gardner (2006) found within a sample of Caucasian same-sex twin pairs, that caffeine intake, heavy caffeine use, and symptoms of caffeine toxicity and dependence to be

associated with an increased risk for developing major depressive disorder (MDD). Also, in 1984, Veleber and Templer found caffeine to increase depression after healthy subjects were administered an affect screener, and in 2011 after a 10-year longitudinal study of 50,730 U.S. women who were previously free of clinical depression at baseline, roughly 5% of the subjects reported a positive correlation between clinical depression and caffeine intake at follow-up (Lucas, Mirzaei, Pan, Okereke, Willett, O'Reilly, Koenen, & Ascherio, 2011). Additionally, those with depressive disorders expressed higher sensitivity to the anxiogenic effects of caffeine despite consuming similar amounts of caffeine as individuals without psychiatric disorders (Lee et al., 1988). Levels of caffeine intake (Greden, Fontaine, Lubetsky, & Chamberline, 1978) and caffeine use in general has been associated with higher depression scores on the Beck Depression Inventory (Dosh et al., 2010). What is also interesting to note is that Greden and colleagues (1980) found that individuals experiencing caffeine-related withdrawal headache report significantly more symptoms of anxiety and depression. However, in conclusion, although several studies have found caffeine to be associated with depression, the causal nature of this association remains uncertain (Kendler et al., 2006).

A family history of substance use problems is another potential correlate of caffeine use and related problems. This relationship has been well established throughout literature, concluding for example, that individuals with a family history of alcoholism are more likely to be alcohol dependent (Svikis et al., 2005). Few studies, however, have directly examined the relationship between family histories of substance abuse/dependence and caffeine consumption. Although, one study conducted by Svikis and colleagues (2005) found that among pregnant caffeine dependent women, those reporting a lifetime diagnosis of caffeine dependence (according to fulfillment of the *DSM-IV* (1994) diagnostic criteria for substance dependence

tailored to caffeine use) and family history of alcoholism had higher rates of caffeine use. Furthermore, the authors found that those with a family history of alcoholism who went on to meet their caffeine dependence criteria were least able to reduce or stop caffeine use during pregnancy (Svikis et al., 2005).

Genetics

Twin and adoption studies have demonstrated genetic factors play a role in alcohol dependence and other substance use disorders (Pickens, Elmer, LaBuda, & Uhl, 1996). Moreover, specific genetic influences may underlie additional risk factors associated with drug use, including personality/psychopathological characteristics, by altering pharmacokinetic or pharmacodynamics mechanisms, or by enhancing other reinforcing effects, such as peer pressure (Pickens, Elmer, LaBuda, & Uhl, 1996).

Much of the human research investigating the etiology of genetic vulnerability to substance abuse has involved twin and adoption studies. Historically, the preponderance of research has focused on alcoholism (e.g., Pickens et al., 1996). However, genetic factors have been found to play a role in the development of other substance use disorders (Heath, Cates, Martin, Meyer, Hewitt, Neale, & Eaves, 1993; Jardine & Martin, 1984; Kaprio, Koskenvuo, & Langinvainio, 1984; Kendler, Heath, Neal, Kessler, & Eaves, 1992; McGue, 1994; Tsuang, Lyons, Eisen, Goldberg, True, Meyer, & Eaves, 1996).

Twin studies of caffeine use and problems have yielded results similar to those found for common licit psychoactive drugs – nicotine (Health et al., 1993; Boomsama, Koopmans, Van Doornen, & Orlebeke, 1994) and alcohol (Kendler et al., 1992; McGue, 1994). Additionally, studies have established common genetic factors underlying the heritable effects of heavy caffeine use in combination with alcohol and nicotine use (Hetterman, Corey, & Kendler, 1999;

Swan, Carmelli, & Cardon, 1996; Swan, Carmelli, & Cardon, 1997). Moreover, recent population-based twin studies have found that similar genetic factors play a role in the development of caffeine and nicotine dependence, but that these genetic influences appear to differ for these licit drugs as compared to illicit drugs (Kendler, Myers & Prescott, 2007; Kendler, Chen, Dick, Maes, Gillespie, Neale, & Riley, 2012), suggesting that a substantial proportion of the genetic influences on caffeine dependence appears to be specific to caffeine alone. Given these findings regarding genetic factors influences the use and dependence of psychoactive drugs, it has been postulated that genetic variation might additionally influence individual differences in caffeine use, toxicity, tolerance, dependence, and withdrawal (Kendler & Prescott, 1999).

A number of twin studies have investigated genetic influences on quantity and frequency of caffeine consumption (Juliano et al., 2009) and have found heritable influences (Carmelli, Swan, Robinette, & Fabsitz, 1990; Conterio & Chiarelli, 1962; Kaprio, Sarna, Koskenvuo, & Rantasalo, 1978; Partanen, Bruun, & Markkanen, 1966; Pedersen, 1981In 1999). Kendler and Prescott (1999) examined the role of genetic factors in the development of caffeine toxicity, tolerance, and withdrawal. They found that among 1,934 female twins, concordance rates for caffeine withdrawal were higher in monozygotic (41%) as compared to same-sex dizygotic (18%) twins, and they estimated heritabilities for caffeine toxicity, tolerance, and withdrawal to range between 35% and 45% (Kendler & Prescott, 1999). The results of this study were replicated in a twin study by Yang, Palmer, and de Wit (2010). In their study, monozygotic twins were found to have higher concordance rates for caffeine consumption than dizygotic twins, with heritabilities ranging from 30% to 77% for caffeine intoxication, withdrawal, and tolerance.

The Cytochrome P450 1A2 (CYP1A2) gene has been shown to be primarily responsible for caffeine metabolism (Gu, Gonzalez, Kalow, & Tang, 1992; Juliano et al., 2014), while the primary gene associated with caffeine use and the effects of caffeine is the ADORA2A gene (codes for the adenosine A_{2a} receptor) (Cornelis, El-Sohemy, & Campos, 2007). Variability in the CYP1A2 gene has been associated with differences in caffeine consumption (Yang et al., 2010; Josse, De Costa, Campos, El-Sohemy, 2012; Rodenburg, Eijgelsheim, Geleijnse, Amin, van Duijn, Hofman, Uitterlinden, Stricker, & Visser, 2012) such that certain allele substitutions within this gene (CYP1A2*1F) attribute to slower caffeine metabolism, while carries of the homozygous for the *1A allele (CYP1A2*1A) are more rapid caffeine metabolizers (Han, Ou-Yang, Lu, Jiang, Shu, Chen, Tan, & Zhou, 2001; Sachse, Brockmoller, Bauer, & Roots, 1999).

A study conducted by Lader and colleagues (1996) also found that slow metabolizers of caffeine were less likely to experience caffeine withdrawal sedation or anxiety after caffeine re-administration. Additionally, Cornelis and coworkers (2006) examined slow versus rapid coffee metabolizers in a group of Costa Rican caffeine users and found isoenzyme differences in their CYP-1A2 gene, also suggesting a genetic basis for differences in caffeine metabolism. These variations in caffeine metabolism have been demonstrated in the literature to be associated with an increased risk for coffee-associated hypertension and myocardial infarction (Cornelis, El-Sohemy, Kabagambe, & Campos, 2006; Palatini, Ceolotto, Ragazzo, Dorigattie, Saladini, Papparelle, Mos, Zanata, & Santonastaso, 2009), in addition to differences in sensitivity and tolerance, meaning the physiological and subjective effects of caffeine may be experienced by some after consuming doses of caffeine substantially lower than that of a regular user (Juliano et al., 2009).

Additionally, polymorphisms of the ADORA2A receptor gene have been associated with caffeine consumption (Juliano et al., 2014), and caffeine's association with psychomotor vigilance (Bodenmann, Hohoff, Freitag, Deckert, Rétey, Bachmann, & Landolt, 2011), anxiety (Childs, Honoff, Deckert, Xu, Badner, & de Wit, 2008; Rogers, Hohoff, Heatherley, Mullings, Maxfield, Evershed, Deckert, & Nutt, 2010), and sleep (Bodenmann et al., 2011; Byrne, Johnson, McRae, Nyhold, Medland, Gehrman, Heath, Madden, Montgomery, Chenevix-Trench, & Martin, 2012; Rétey, Adam, Khatami, Luhmann, Jung, Berger, & Landolt, 2007) (Juliano et al., 2014). Genetic factors also "appear to substantially influence a woman's vulnerability to caffeine use, heavy use, intoxication, tolerance, and withdrawal" (p. 226, Kendler & Prescott, 1999). Overall, the genetic data presented above highlights the underlying biological basis for caffeine use and its associated problems (Juliano, et al., 2009); however, research has not identified specific genes that increase an individual's vulnerability specific to caffeine withdrawal syndrome (APA, 2013).

Statement of Problem

Like many psychoactive substances, daily use of caffeine can lead to dependence and abrupt cessation of use can produce symptoms of withdrawal. Research findings have provided significantly robust evidence to include caffeine withdrawal in the *DSM-5* (APA, 2013). The incidence of clinically significant distress or functional impairment as a result of caffeine withdrawal in normal subjects varies from 10% to 55%, with a median of 13% (Juliano & Griffiths, 2004). Many consider headaches to be the hallmark symptom of withdrawal among regular caffeine users, with 11% of caffeine consumers reporting headaches and at least on other symptom following caffeine abstinence (Juliano et al., 2014).

While the symptoms of caffeine withdrawal have been characterized, not all chronic caffeine users experience caffeine withdrawal during periods of caffeine abstinence. Much less is known about other correlates (predictors) of caffeine withdrawal (Hughes et al., 1993; Juliano & Griffiths, 2004), providing little evidence regarding the variability in risk for having headaches and other symptoms of caffeine withdrawal. For example, Juliano and Griffiths (2004) stated that "very little is known about the determinants of individual differences in caffeine withdrawal" (p. 23). Furthermore, only a few studies exist examining treatment for caffeine use, including best practices to promote caffeine reduction and cessation (Meredith et al., 2013).

To advance the caffeine withdrawal literature, the present study will examine prevalence rates of recent caffeine in males and females, looking separately at coffee, tea, soda, energy drinks, energy shots, and other forms of caffeine use as well as symptoms of caffeine withdrawal. In addition, univariable analyses will be used to identify psychosocial factors associated with caffeine withdrawal headache (CWH), drawing not only from caffeine use frequency measures but also personal and parental histories of alcohol use and problems, as well as symptoms of depression and anxiety and other psychosocial factors. These findings will also be examined separately for males and females, a novel methodological approach in the field of caffeine withdrawal research. It is hypothesized that the likelihood of experiencing a CWH will not only increase as frequency of caffeine use (days/weeks) increases, but that daily caffeine users will also be more likely to report CWH than non-daily caffeine users. The ability to identify the predisposing factors associated with caffeine dependence and related problems are of paramount importance so that education can be targeted to prevent and treat those at risk for

caffeine dependence. This information may also inform future development of tailored prevention and intervention programs targeting caffeine and other substance use in young adults.

Caffeine is considered the most widely used psychoactive drug in the world, but because caffeine concentration varies considerably within and across foods and beverages, researchers have struggled to develop effective methods to assess caffeine consumption frequently and accurately (Addicott et al., 2009; Meredith et al., 2013). In particular, quantity of caffeine consumed has been difficult to measure without a detailed assessment. Such interviews are labor intensive and often not practical in survey research. As a result, many studies rely solely upon retrospective frequency measures of caffeine use. The present study also examined validity of self-report frequency measures of caffeine consumption by examining their relationship to the experience of a caffeine withdrawal headache. This information will help inform methods for developing accurate caffeine consumption assessments in future research.

Aims and Hypothesis

The present study used year 1 freshman cohort data from the Virginia Commonwealth University (VCU) Spit for Science project to examine caffeine use patterns and psychosocial factors associated with self-reports of caffeine withdrawal. Given that headaches are the hallmark feature of caffeine withdrawal, headaches after cessation of caffeine use for a day or more served as the primary dependent outcome measure. The present study had 2 specific aims. First (Aim 1), prevalence rates of recent caffeine use were examined in males and females, looking separately at coffee, tea, soda, energy drinks, energy shots, and other forms of caffeine use as well as symptoms of caffeine withdrawal. Second (Aim 2), univariable analyses were used to identify psychosocial factors associated with caffeine withdrawal headache (CWH).

Those significant at $p \leq .25$ were then examined together using multiple backward stepwise regression and other modeling approaches to identify a final parsimonious model.

This study tested 2 hypotheses: Hypothesis 1: Likelihood of experiencing a CWH would increase as frequency of caffeine use (days/weeks) increased. Hypothesis 2: Daily caffeine users would be more likely to report CWH than non-daily caffeine users.

Methods

Data set

The present study utilized the 2011 freshman survey collected as part of the Spit for Science project, which was funded by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) (Kendler & Dick; NIH R37 AA011408). This university-wide survey was administered to undergraduate students attending a large, urban, public university in Richmond, Virginia. The overall purpose of the Spit for Science project was to understand how genetic influences interact with environmental and developmental influences to impact substance use and emotional health outcomes in college students. The Spit for Science baseline survey queried college freshman about alcohol and other substance use, as well as mental health, personality, and a variety of behavioral and life experiences, with follow-up surveys at the end of each participant's freshman, sophomore, junior, and senior year. In addition, DNA samples were obtained, providing an opportunity to examine how genetic factors contribute to the development of alcohol use disorders and other mental health problems. [See Dick et al., (2014) for a full description of the Spit for Science project].

Participants

The present sample included N = 2,056 freshmen who participated in the Fall, 2011 Spit for Science baseline survey. The survey response rate was 57%, with 97% (n = 1884) of

participants also providing a saliva sample for DNA analysis. Only students over the age of 18 were eligible for the study. Demographically, over half the sample was female (57%), with 50% White, 20% African American, 15% Asian, and 7% Hispanic.

Study Procedures

Recruitment began with information about the study being mailed to all incoming freshmen and (separately) to their parents. Then, during the week before "Welcome Week," all freshmen over age 18 received an invitation via their university e-mail account to participate in the survey. The invitation e-mail contained a link to the online survey. E-mail reminders were also sent to non-responders. Upon completion of the survey, students went to a central site at the university to collect compensation ($10 and a free Spit for Science t-shirt). At that time, they were also invited to provide a saliva DNA sample for which they received an additional $10.

Informed Consent

Informed consent was obtained separately for the online survey and DNA sample and students could participate in just the survey portion of the project or both the survey and DNA components.

Data and DNA Collection

Study data were collected and managed using REDCap, a secure, web-based application designed to support data capture for research studies. Oragene collection tubes were used to obtain four milliliters of saliva from each participant (DNA Genotek, Kanata, Ontarios). DNA was isolated from these samples following manufacturer's instructions, and each isolation sample was quantified by spectrophotometry using a Thermo Nanodrop (Thermo Fisher Scientific, Waltham, MA). [Further details regarding these Spit for Science procedures can be found in Dick et al., 2014].

Measures

The baseline survey required 15-30min. to complete and focused on the domains listed in Table 4 (in order presented during the online survey). The response options to each question varied but participants were able to skip (not answer) specific questions. Potential correlates of CWH were selected from the domains noted with an asterisk (Table 4) and are summarized further in the following paragraphs.

Demographics

Participants provided their date of birth, gender (male, female), and race (response options included: American Indian/Alaska Native; Asian; Black/African American; Hispanic/Latino; More than one race; Native Hawaiian/Other Pacific Islander; Unknown; White).

Recent Caffeine Use

Participants were asked, "Do you drink any caffeinated beverages?" This included instant or filtered/brewed coffee, tea (e.g., sweet, green, black, and others), caffeinated sodas (e.g., Coke, Pepsi, Mountain Dew), energy drinks (e.g., Red Bull, Monster, Rock Star), and energy shots (e.g., 5-Hour Energy)." Participants who answered yes were then asked about frequency of caffeine use (past 30 days), with separate queries for each of the following caffeine sources: coffee; hot or cold tea; caffeinated sodas; energy drinks; energy shots, and other caffeine-containing beverages. Response options ranged from 0 (not at all) to 7 days/week (daily, or almost daily). Participants were also asked separately about frequency of use of over-the-counter caffeinated medicines (e.g., Vivarin, NoDoz, Excedrin, Vanquish, Anacin, Dristan).

Table 4.

Spit for Science Survey Domains.

Domains	*Measure*
Demographics*	Age, race, and gender
Personality*	Big Five Inventory
Alcohol Use*	Varied items
Alcohol Expectancies	B-CEOA
Drinking Motives	Drinking Motives Questionnaire
Reasons for Not Drinking	Varied items
Parenting Styles	Parenting Styles Inventory
Family History*	Varied items
Life Events	Life Events Checklist
Caffeine Use*	Varied items
Peer Group Deviance	Varied items
Nicotine Use*	Varied items
Illicit Drug Use	Varied items
Antisocial Behavior	SSAGA
Religiosity	National Comorbidity Survey
Anxiety/Depression*	SCL-90
Binge Eating	EDE-Q

Note: SSAGA = Semi-Structured Assessment for the Genetics of Alcoholism; B-CEO-A = Brief Comprehensive Effects of Alcohol; SCL-90 = Symptom Checklist -90; EDE-Q = Eating Disorder Examination Questionnaire.

Caffeine Withdrawal

Participants reporting any recent caffeine use were asked about symptoms of caffeine withdrawal experienced after cessation of caffeine for a day or more. Symptoms included: Headache, Fatigue, Anxiety, Depression, and Nausea or Vomiting.

Alcohol Use and Problems

Participants who reported ever drinking alcohol (excluding small tastes and sips) proceeded to answer questions about recent frequency of use (days drank in the past 30) and quantity consumed (number of drinks consumed on recent days drinking). Participants also selected the category that best described their drinking, with response options that included: Abstainer, Abstainer – former problem drinker in recovery, Infrequent drinker, Light drinker,

Moderate drinker, Heavy drinker, and Problem drinker. Additionally, participants reported separately on how many of their peers a.) "drank alcohol," b.) "got drunk," and c.) "had problems with alcohol (like hangover, fights, accidents)." For all 3 questions, participants had 5 response options: None, A few, Some, Most, or All. Participants were also asked if they had ever become tolerant to alcohol (defined as drinking a great deal more in order to get an effect, or found you could no longer get buzzed on the amount you used to drink). Response options included: Yes, No, or Don't Know.

Lifetime Cigarette Smoking

Participants were asked to estimate how many cigarettes they had smoked (lifetime), with the following response options: None, 1 – 9, 10 – 99, 100 – 200, or More than 200. If the participant responded "None" then they were not asked subsequent questions regarding nicotine use.

Recent Use (cigarettes and other tobacco products)

Recent frequency of cigarette smoking was assessed for past 30 days, with response options of: Once or twice, A few days (3-4 days a month), A couple of days a week (5 to 11 days a month), Three times a week (12 to 14 days a month) Most days of the week (15 to 25 days a month), or, Daily or almost daily (26 to 30 days a month). Number of cigarettes smoked per day was also assessed, with response options of: 10 or less, 11 – 20, 21 – 30, or 31 or more. Additionally, participants were asked about their recent (past 30 days) use of other nicotine products (i.e., cigar, little cigar, cigarillos (e.g., Black & Mild), and hookah), with the same response options as for cigarettes. Additionally, they were asked how many of their peers smoked cigarettes over the past year, with 5 response options: None, A Few, Some, Most, or All.

Psychopathology

The present study focused on two subscales of the Symptom Checklist-90 (SCL-90) (Derogatis, Lipman, & Covi, 1973); anxiety (7-items; α=0.85) and depression (11-items; α=0.89). The SCL-90 is a well-recognized tool for identification of psychopathology and has been used in numerous studies as an indicator of mental health (Derecho, Wetzler, McGinn, Sanderson, & Asnis, 1996; Hauff & Vaglum 1995; Koh, Kim, & Park, 2002; Preston, Orr, Data, Nolan, & Castle, 2002). It is particularly useful as a measure of mental health status in non-psychiatric settings (Boudrez & De Basker 2001, Osterberg, Karlson, & Orbaek, 2002; Skydsbjerg, Lunn, & Hutchings, 2001; Yang, 2001). Each item is scored on a five-point Likert scale, ranging from Not at all (1) to Extremely (5).

Personality

Personality was measured using the Big Five Inventory (BFI; John & Srivstava, 1999), a self-report instrument designed to measure the following 5 personality dimensions: Extraversion (8-items; α = .84), Agreeableness (9-items; α = .76), Conscientiousness (9-items; α = .79), Neuroticism (8-items; α = .81), and Openness (10-items; α = .74). The BFI is a reliable and valid measure of personality (Benet-Martínez & John, 1998; John, Naumann, & Soto, 2008; Rammstedt & John, 2007; Soto, John, Gosling, & Potter, 2008; Srivastava, John, Gosling, & Potter, 2003). Participants responded to each of the 44 items on a 5-point Likert scale ranging from 1 (Disagree strongly) to 5 (Agree strongly).

Family history

Participants were asked to report on maternal and paternal alcohol and/or drug problems (defined as drinking/drug use causing problems at home, at work, with their health, or with the police, or that they received alcohol/drug treatment). Response options included: Yes, No, and I

Don't Know. Participants were also asked to report on maternal and paternal depression or anxiety symptoms, with similar response options of: Yes, No, and I Don't Know.

Study Variables

Caffeine use. For the present study, only those participants who responded yes or no to question, "Do you drink caffeinated beverages?" were included in the analyses. If a participant responded "No" to the question "Do you drink caffeinated beverages," they would then skip out of questions "In the last month in a typical week on how many days did you drink coffee, tea, …take over-the-counter caffeinated medicines?" Therefore, these responses were recoded "0 days." The present study focused specifically on coffee, tea, soda, energy drink, energy shot, other caffeinated beverage, and over-the-counter caffeinated medicine use. Variables included: **Caffeine users**: defined as those reporting consuming at least one of the caffeinated products one day per week in the past month. **Frequency of caffeine use**: days of use in a typical week during the past month, separately for: coffee; hot or cold tea; caffeinated sodas; energy drinks; energy shots, and other caffeine-containing beverages. **Recent daily caffeine users**: categorical (yes/no) for consuming daily (7 days per week in the past month) for the same 7 caffeine-containing beverage types and medications. **Daily use/any caffeine**: categorical (yes/no), defined as those reporting consuming at least one of the caffeinated beverage types daily in the past month.

Caffeine Withdrawal. Caffeine withdrawal headaches were selected as the hallmark symptoms of caffeine withdrawal. Other symptoms of caffeine withdrawal were also examined, including: fatigue; anxiety; depression, and nausea/vomiting. In the analyses, response options and coding were as follows: yes = 1/no = 0. If a caffeine user reported "None, Don't know, never quit," or "I choose not to answer," to the question "If you quit all caffeine for a day or

more, do you experience any of the following withdrawal symptoms (headache, fatigue, anxiety, depression nausea or vomiting), they were coded as experiencing "No" withdrawal symptoms.

Alcohol Use and Problems. Continues variables included: **Frequency of alcohol use**: days of alcohol use in a typical week during the past month; **Quantity of alcohol use**: number of drinks consumed on recent drinking days, and **Total amount of alcohol consumed**: days of alcohol use in the past 30 multiplied by number of drinks consumed on drinking days. Categorical variables included: **Current drinking type**: participant self-attribution, with response options combined to create 4 categories: Non-users (abstainers); Minimal Users (infrequent and light drinkers); Moderate Users (moderate drinkers), or Heavy/Problem Users (heavy drinkers + problem drinkers + former problem drinkers); **Alcohol tolerance** (need to drink more alcohol to get the same effect): categorical (yes/no), and **Peer alcohol problems**: response items were combined to create 3 categories: None, A Few or Some of them, and Most of All of them.

Nicotine Use. Categorical variables included: **Lifetime tobacco use (cigarettes)**: 3 categories were created: 0 cigarettes (never smoked); 1-99 cigarettes, or 100+ cigarettes; **Recent cigarette use and other tobacco use (cigar, little cigar, cigarillos e.g., Black & Mild; hookah)**: responses options for **recent cigarette use** were subsequently combined to create 4 categories: none, once or twice, or multiple days per month (3-25 days a month), or daily or almost daily (26 to 30 days a month); response options for **recent other tobacco use** were combined to create 3 categories: none, once or twice, or multiple days per month (3-25 days a month), and **Peer smoking (cigarettes)**: response items were combined to create 3 categories: None, A Few or Some of them, and Most of All of them.

Psychopathology. Total scores for anxiety and depression scales were calculated (controlling for missing information). This yielded a raw score, which determined the severity of the participants' symptoms for that scale.

Personality. Scale scores for each item, ranging from 1 (Disagree strongly) to 5 (Agree Strongly), were summed to yield a "score" for each of the five personality factors. Higher scores indicated more of the trait being measured.

Parental History. Parental history measures included: maternal alcohol, drug, depression or anxiety; and paternal alcohol, drug, and depression or anxiety. Responses were subsequently dichotomized (yes = 1/no = 0; with "I Don't Know" coded as missing).

Data Analyses and Procedures

This investigation utilized pre-existing data collected through the Spit for Science freshman survey for 2011 (described above). Statistical analyses were performed using SPSS v.23.0 (SPSS, Chicago, IL). Prior to analysis, frequency patterns of all variables of interest were prepared and screened for missing values. Additionally, means, standard deviations, and 95% confidence intervals (or medians and inter-quartile ranges) were computed for each continuous variable, as well as frequencies, proportions and 95% confidence intervals for each categorical variable.

To select variables that will result in a "best" model within the context of this study, univariable regression models and chi-square analyses tests were performed within a priori hypothesized domains (demographics, caffeine use, alcohol use, nicotine use, anxiety/depression, personality, and family history of drug/alcohol use and depression/anxiety) to identify variables associated with CWH. Each analysis was performed separately for males and females.

A multivariable logistic regression model building strategy proposed by Mickey and Greenland (1989) was used to build a parsimonious model for predicting CWH. The significance level was set higher than conventional levels to increase the likelihood the multivariable logistic regression analyses performs acceptably. Variables meeting a ≤ 0.25 p-value significance test were considered for the multivariate logistic regression analysis (Mickey & Greenland, 1989). In the first stage, all univariable regression models were tested using each potential predictor on CWH with particular attention paid to the nature of the relationship between CWH and each predictor. In the second stage, all predictors demonstrating at least a moderate ability to predict CWH ($p \leq .25$) became candidate predictors in a multiple backward stepwise regression algorithm. This approach was used to remove all main effects found not predictive ($p > .05$). This model was considered the final model.

Aim 1: Examine prevalence rates of recent caffeine consumption in the sample of college freshmen. To address the first study aim, frequency patterns of caffeine consumption and beverage intake patterns were created, separately for both males and females. Frequency patterns of caffeine withdrawal symptoms were also summarized. Following these descriptive analyses each hypothesis was tested systematically.

Hypotheses:

A univariable logistic regression analysis was used to examine hypothesis one: the likelihood of experiencing a CWH would increase as frequency of caffeine use (days/weeks) increased. Chi-square analyses were performed to examine hypothesis two: daily caffeine users would be more likely to report CWH than non-daily caffeine users.

Aim 2: Univariable and multivariable analyses were used to identify variables associated with caffeine withdrawal headache. To address the second aim, univariable

regression and chi-square analyses were used to identify demographic and psychosocial variables associated with CWH. Variables meeting a $p \leq 0.25$ level of significance where then entered into a multivariable logistic regression and a backwards elimination procedure was used to arrive at a parsimonious model for predicting CWH. In the final model the only variables that remained were significant at the $p \leq 0.05$ level.

Results

Demographic Correlates of Caffeine Use

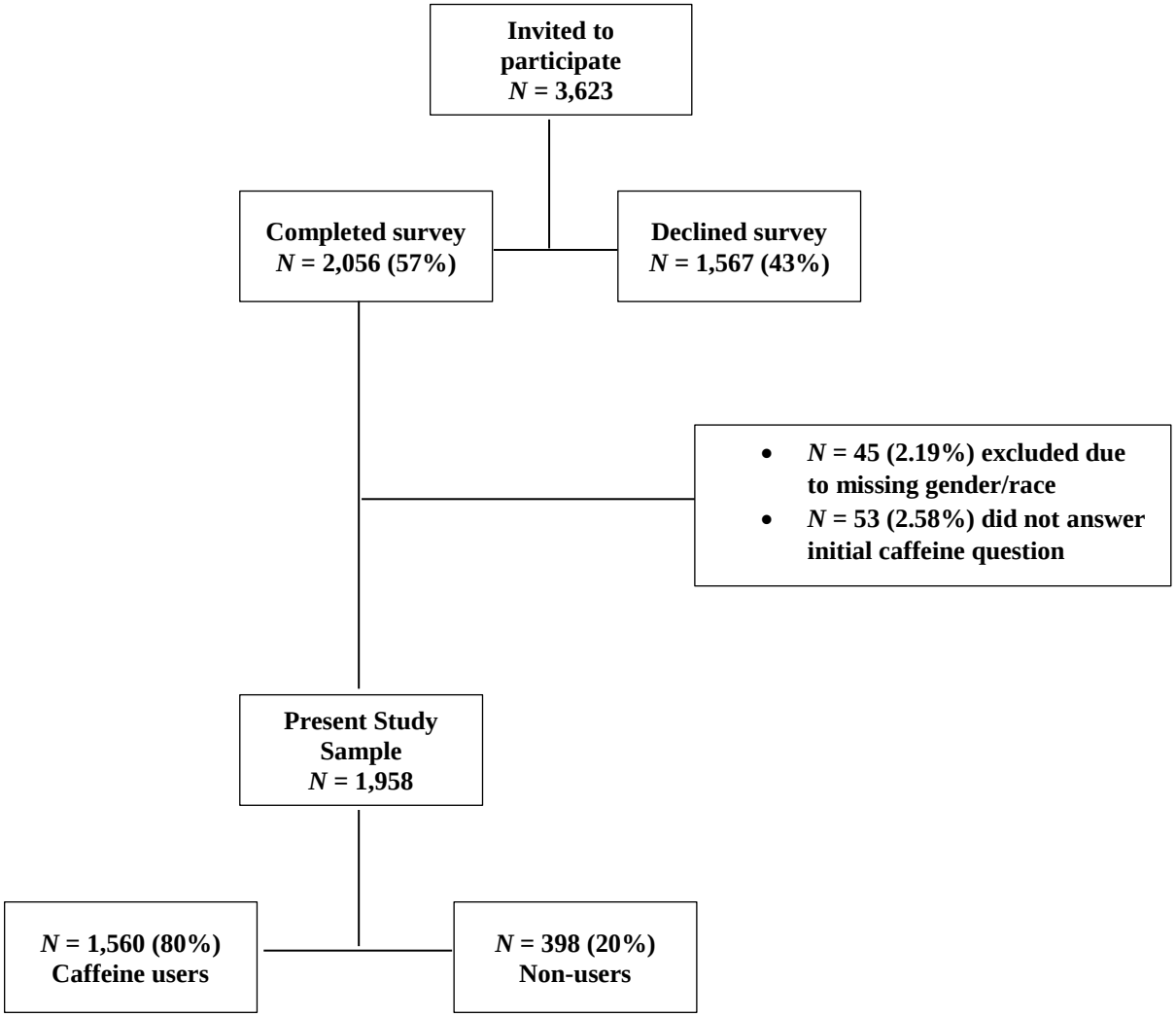
Invitations to participate were sent to 3623 individuals across the fall data collection period. A total of 2056 individuals (57%) completed the survey; survey completion was considerably higher among on-campus freshman (62%) than among off-campus freshmen (36%). From the full cohort of 2011 freshmen (N = 2,056) (*n* = 45) were excluded due to missing data (gender and/or race), and another (*n* = 53) were excluded because they did not answer the question, "Do you drink any caffeinated beverages?" leaving a final sample size of N = 1958 for Analyses (Figure 1).

Descriptive statistics for the final sample and separately for those with and without CWH's are summarized in Table 5. Because of the low endorsement rates of CWH among minority groups, the decision was made to consolidate the responses of all minority group members (American Indian/Alaska Native; Asian; Black/African American; Hispanic/Latino; More than one race; and Native Hawaiian/Other Pacific Island) and categorize those responses as "non-White" (see Table 5). Race will be included in the multivariable analyses. Due to the significant differences in reported CWH, subsequent analyses are presented by gender.

As shown in Table 5, the sample of N = 1958 had a mean (M) age of 18.5 years (*SD* = .61), and nearly two-thirds (61%) were female (*n* = 1200). Approximately one-half (53%)

Figure 1.

Spit for Science recruitment and enrollment consort diagram.



identified as White (*n* = 1031), and 47% were classified as non-White (*n* = 927). Nearly 80% reported drinking caffeinated beverages. That is, in the sample of N = 1958 study participants who responded to the item, "Do you drink any caffeinated beverages?" N = 1560 responded yes, and of these participants, nearly two-thirds (65.3%) were female (*n* = 1019), and over half (55.8%)

were White (n = 870). Among these participants, 15.4% (n = 241) reported CWH, and approximately three-fourths of this subgroup was female (74%; n = 179).

Table 5.

Demographic Characteristics of All Caffeine Users and Participants with and without CWH.

	Total Sample % or M (SD) (n = 1958)	CWH Yes % or M (SD) (n = 241)	CWH No % or M (SD) (n = 1717)	*CWH* X^2	*CWH* *p*
Age (years)	18.5 (.61)	18.5 (.69)	18.5 (.60)		
Gender	---	---	---	19.54	< .001
Male	38.7	25.7	40.5		
Female	61.3	74.3	59.5		
Race	---	---	---		
Caucasian	52.7	79.3	48.9		
African American	19.4	5.8	21.3		
Hispanic/Latino	5.9	4.1	6.2		
Asian	15.2	4.1	16.8		
American Indian/Alaska Native	0.5	1.2	0.4		
Native Hawaiian/Other Pacific Islander	0.8	0.4	0.8		
More than one race	5.5	5.0	5.6		
White vs. non-White	---	---	---	77.99	< .001

Aim 1: Prevalence of recent caffeine use and withdrawal by beverage type and gender.

Caffeine Use

Eighty percent (n = 1560) of the sample reported recent caffeine use (see Table 6), with females more likely to use caffeine than males ($\chi 2$ (1) = 52.63; p < .001). Prevalence rates varied by beverage type, with two-thirds of the sample drinking sodas (65.7%), followed by tea (54.2%) and coffee (51.6%). Prevalence of energy drink and/or shot use was lower (16% and 4%, respectively). Females were more likely to drink coffee (p < .001), tea (p < .001), soda (p = .042) and other caffeinated beverages (p = .004), and more likely to report use of caffeinated medicines (p = .019) than males.

Table 6.

Prevalence of Recent Caffeine Use by Gender and Beverage Type.

Caffeine Source	*Sample N (%) (n = 1958)*	*Males N (%) (n =758)*	*Females N (%) (n =1200)*	*χ2*	*df*	*p*
Any Caffeine Use	1560 (79.7)	541 (71.4)	1019 (84.9)	52.63	1	< .001
Coffee	1011 (51.6)	297 (39.2)	714 (59.5)	76.80	1	< .001
Tea	1062 (54.2)	341 (45.0)	721 (60.1)	42.66	1	< .001
Soda	1286 (65.7)	477 (62.9)	809 (67.4)	4.15	1	.042
Energy Drinks	313 (16.0)	141 (18.6)	172 (14.4)	6.29	1	.012
Energy Shots	78 (4.0)	35 (4.6)	43 (3.6)	1.30	1	.254
Other Caffeinated Beverages	350 (17.9)	112 (14.8)	238 (19.8)	8.10	1	.004
Caffeinated Medicines	122 (6.2)	35 (4.6)	87 (7.2)	5.51	1	.019

Frequency of Caffeine Use by Gender and Beverage Type

For each caffeine beverage type, frequency of use (days used on a typical week in the past month) is summarized in Table 7. For the full sample, daily use was most prevalent for sodas (12.8%), followed by tea (9.0%) and then coffee (6.4%), with far fewer students reporting daily use of energy drinks (0.7%) and other types of caffeine. This pattern was found for both males and females.

Table 7.

Frequency of Caffeine Use by Gender and Beverage Type (N = 1958).

Caffeine Source	*0 Days/ Week*	*1 Day/ Week*	*2 Days/ Week*	*3 Days/ Week*	*4 Days/ Week*	*5 Days/ Week*	*6 Days/ Week*	*7 Days/ Week*
Coffee								
%Total	48.2	14.7	10.3	8.4	6.4	3.5	2.2	6.4
%Male	60.7	10.6	7.7	6.8	5.0	2.5	0.9	5.8
%Female	40.3	17.3	12.0	9.4	7.3	4.1	3.0	6.7

Tea								
%Total	45.6	10.3	10.7	9.7	6.1	6.0	2.6	8.9
%Male	55.0	10.2	9.8	7.1	5.0	3.8	1.6	7.5
%Female	39.8	10.4	11.4	11.3	6.8	7.4	3.2	9.8
Soda								
%Total	34.2	9.7	11.9	11.6	9.3	7.1	3.5	12.8
%Male	37.0	7.1	10.2	12.8	9.2	6.7	3.6	13.3
%Female	32.5	11.3	13.0	10.9	9.3	7.3	3.4	12.4
Energy Drinks								
%Total	84.0	8.2	3.1	1.7	1.3	0.8	0.1	0.7
%Male	81.4	9.8	3.2	2.1	1.7	1.2	0.0	0.7
%Female	85.6	7.3	3.1	1.5	1.1	0.6	0.2	0.7
Energy Shots								
%Total	96.0	2.5	0.7	0.3	0.3	0.1	0.1	0.1
%Male	95.4	3.0	0.9	0.3	0.3	0.0	0.1	0.0
%Female	96.4	2.2	0.5	0.3	0.3	0.2	0.0	0.2
Other Caffeinated Beverages								
%Total	81.9	4.5	5.2	3.0	2.1	0.9	0.4	1.9
%Male	85.1	3.9	5.1	1.9	1.5	0.9	0.3	1.5
%Female	80.0	5.0	5.2	3.8	2.5	0.8	0.4	2.3
Caffeinated Medicine								
%Total	93.7	2.4	1.4	0.7	0.7	0.5	0.1	0.4
%Male	95.4	1.7	1.2	0.8	0.3	0.1	0.0	0.5
%Female	92.7	2.8	1.6	0.7	0.9	0.8	0.2	0.3

Caffeine Withdrawal

As displayed in Table 8, approximately one-fifth of the sample of caffeine users reported symptoms of caffeine withdrawal (20.4%). Headaches were most prevalent (15.4%), followed by fatigue (12.9%); anxiety (3.6%); depression (1.7%) and nausea/vomiting (1.0%). Symptom prevalence differed by gender, with females more likely than males to report headaches (17.6% vs. 11.5%, $\chi 2$ (1) = 10.09; $p < .001$) and fatigue (14.8% vs. 9.2%, $\chi 2$ (1) = 9.79; $p < .001$). Females were also more likely than males to report one or more symptoms of caffeine withdrawal (22.9% vs. 15.9%, $\chi 2$ (1) = 10.55; $p < .001$).

Table 8.

Caffeine Withdrawal Symptoms by Gender.

Caffeine Withdrawal Symptom	*Sample N (%)* (*n* = 1560)	*Males N (%)* (*n* = 541)	*Females N (%)* (*n* = 1019)	*χ2*	*df*	*p*
Headache	241 (15.4)	62 (11.5)	179 (17.6)	10.09	1	.001
Fatigue	201 (12.9)	50 (9.2)	151 (14.8)	9.79	1	.002
Anxiety	56 (3.6)	13 (2.4)	43 (4.2)	3.37	1	.066
Depression	26 (1.7)	5 (0.9)	21 (2.1)	2.79	1	.095
Nausea/Vomiting	16 (1.0)	5 (0.9)	11 (1.1)	0.08	1	.772
1+ Symptom	319 (20.4)	86 (15.9)	233 (22.9)	10.55	1	.001

Aim 1/Hypothesis 1 and 2:

Hypothesis 1: the likelihood of experiencing a CWH will increase as frequency of caffeine use (days/weeks) increases:

Hypothesis 1: results of the univariable regression analysis for the whole sample and separately for males and females are summarized in Table 9 for each of the 7 caffeine sources (coffee, tea, soda, energy drinks, energy shots, other caffeinated beverages, and caffeinated medicines) and CWH.

Overall, as frequency of nearly every caffeine source increased the likelihood of experiencing a CWH also increased. When examined separately by gender, there were three significant OR's in males for coffee (1.32), tea (1.20), and soda (1.17) users. For females, significant OR's were found for all caffeine beverage types with OR's ranging from 1.07 for tea to 1.47 for coffee, and 1.38 for caffeine-containing medicines. Taken together, Hypothesis

Table 9.

Univariable Regression Model of Frequency of Caffeine Use Predicting Caffeine Withdrawal Headache (*N*=1560)

Variables	*B*	*S.E.*	*Wald*	*df*	*p*	*Odds Ratio*	*95% C.I. for Ex(B)*	
							Lower	*Upper*
Coffee use	.352	.030	135.30	1	< .001	1.42	1.34	1.51
Males	.279	.054	26.82	1	< .001	1.32	1.19	1.47
Females	.383	.037	105.32	1	< .001	1.47	1.36	1.58
Tea use	.108	.028	14.63	1	< .001	1.12	1.05	1.18
Males	.178	.053	11.28	1	.001	1.20	1.08	1.33
Females	.072	.034	4.51	1	.034	1.07	1.01	1.15
Soda use	.140	.029	22.60	1	< .001	1.15	1.09	1.22
Males	.158	.060	7.00	1	.008	1.17	1.04	1.32
Females	.151	.034	19.43	1	< .001	1.16	1.09	1.24
Energy drink use	.192	.052	13.76	1	< .001	1.21	1.10	1.34
Males	.142	.092	2.39	1	.122	1.15	0.96	1.38
Females	.246	.065	14.43	1	< .001	1.28	1.13	1.45
Energy shot use	.190	.111	2.93	1	.087	1.21	0.97	1.50
Males	-.043	.290	.02	1	.881	0.96	0.54	1.69
Females	.260	.127	4.19	1	.014	1.30	1.01	1.66
Other caffeinate beverage use	.169	.039	18.85	1	< .001	1.18	1.10	1.28
Males	.055	.088	.39	1	.531	1.06	0.89	1.26
Females	.200	.045	19.73	1	< .001	1.22	1.12	1.33
Caffeinate medicine use	.241	.064	14.42	1	< .001	1.27	1.12	1.44
Males	-.122	.216	.32	1	.574	0.89	0.58	1.35
Females	.323	.074	18.83	1	< .001	1.38	1.19	1.60

1 was supported with the likelihood of CWH increasing with increasing frequency of use for all 7 caffeine sources in females and 3 of 7 caffeine sources in males.

Hypothesis 2: Daily caffeine consumers will be more likely to report caffeine withdrawal headaches than non-daily caffeine consumers:

Hypothesis 2: This hypothesis was tested separately for each caffeine source, looking at the total sample of caffeine users as well as separately by gender. For caffeine overall and

Table 10.

Chi-square Analyses Comparing Daily and Non-daily Caffeinated Beverage Use and CWH.

Sample	Daily Caffeine Drinkers N (%)	Non-Daily Caffeine Drinkers N (%)	*χ2*	*df*	*p*
Full Sample (1560)	467 (29.9)	1093 (70.1)	----	----	----
CWH (241)	142 (30.4)	99 (9.1)	114.17	1	< .001
Males (541)	168 (31.1)	373 (68.9)	----		----
CWH (62)	44 (26.2)	18 (4.8)	52.11	1	< .001
Females (1019)	299 (29.3)	720 (70.7)	----		----
CWH (179)	98 (32.8)	81 (11.3)	67.60	1	< .001
Sample	Daily Coffee Drinkers N (%)	Non-Daily Coffee Drinkers N (%)	*χ2*	*df*	*p*
Full Sample (1560)	124 (7.9)	1436 (92.1)	----	----	----
CWH (241)	68 (54.8)	173 (12.0)	160.01	1	< .001
Males (541)	44 (8.1)	497 (91.9)	----		----
CWH (62)	18 (40.9)	44 (8.9)	40.94	1	< .001
Females (1019)	80 (7.9)	939 (92.1)	----		----
CWH (179)	50 (62.5)	129 (13.7)	121.05	1	< .001
Sample	Daily Tea Drinkers N (%)	Non-Daily Tea Drinkers N (%)	*χ2*	*df*	*p*
Full Sample (1556)	175 (11.2)	1381 (88.8)	----	----	----
CWH (241)	39 (22.3)	202 (14.6)	6.96	1	.008
Males (540)	57 (10.6)	483 (89.4)	----		----

CWH (62)	14 (24.6)	48 (9.9)	10.73	1	.001
Females (1016)	118 (11.6)	898 (88.4)	----		----
CWH (179)	25 (21.2)	154 (17.1)	1.17	1	.279

Sample	Daily Soda Drinkers N (%)	Non-Daily Soda Drinkers N (%)	χ^2	*df*	*p*
Full Sample (1557)	250 (16.1)	1307 (83.9)	----	----	----
CWH (241)	66 (26.4)	175 (13.4)	27.15	1	< .001
Males (540)	101 (18.7)	439 (81.3)	----		----
CWH (62)	23 (22.8)	39 (8.9)	15.58	1	< .001
Females Only (1017)	149 (14.7)	868 (85.3)	----		----
CWH (179)	43 (28.9)	136 (15.7)	15.26	1	< .001

Sample	Daily ED Drinkers N (%)	Non-Daily ED Drinkers N (%)	χ^2	*df*	*p*
Full Sample (1557)	13 (0.8)	1544 (99.2)	----	----	----
CWH (241)	2 (15.4)	239 (15.5)	0.00	1	.993
Males (540)	5 (0.9)	535 (99.1)	----		----
CWH (62)	1 (20.0)	61 (11.4)	0.36	1	.548
Females (1017)	8 (0.8)	1009 (99.2)	----		----
CWH (179)	1 (12.5)	178 (17.6)	0.15	1	.704

Sample	Daily OCB Drinkers N (%)	Non-Daily OCB Drinkers N (%)	χ^2	*df*	*p*
Full Sample (1541)	38 (2.5)	1503 (97.5)	----	----	----
CWH (236)	15 (39.5)	221 (14.7)	17.53	1	< .001
Males (533)	11 (2.1)	522 (97.9)	----		----
CWH (60)	2 (18.2)	58 (11.1)	0.54	1	.463
Females (1008)	27 (2.7)	981 (97.3)	----		----
CWH (176)	13 (48.1)	163 (16.6)	18.13	1	< .001

Note: ED = Energy Drinks; OCB = Other Caffeinated Beverages

separately for all other caffeine sources, results are summarized in Table 10. Female daily users of one or more forms of caffeine were 3 times more likely to report CWH than females not reporting daily use of any caffeine product ($p < .001$). For males, CWH's were 6 times more likely to occur in daily as compared to non-daily caffeine users ($p < .001$). For individual caffeine beverage types, prevalence of daily use varied from 16.1% for sodas, followed by 11.2% for tea, and 7.9% for coffee. Prevalence rates for energy shot use and caffeinated medicine use was even lower. Because of the low rates of daily use, caffeine energy shots and caffeinated medicines were not compared (N = 2, 0.1% for energy shots and N = 8, 0.5% for caffeinated medicine use).

For the total sample, Hypothesis 2 was confirmed for caffeine overall as well as for 4 of the 5 caffeine beverage types, not including caffeine energy shots and caffeinated medicines. Only energy drinks did not show this pattern, in part because of the low prevalence of daily ED use (N = 13 individuals; 0.8%). The pattern was largely consistent in both females and males, excluding tea for females and other caffeinated beverages for males.

Aim 2: Univariable and multivariable analyses identifying variables associated with caffeine withdrawal headache.

Alcohol

The number of caffeine-using participants who also reported having at least one alcoholic drink in their entire life was 1151 (73.8%). Participants who reported recent alcohol use (N = 983; 63.0%) reported drinking a mean of 3.5 days in the past 30 days (SD = 4.8), with an average of 3.7 (SD = 4.5) drinks consumed per drinking occasion (Table 11). Of these participants who drank, most self-described as light drinkers (45.3%), with 16.4% as moderate drinkers, 36.1% as abstainers, and 2.2% as heavy or problem drinkers (Table 12). Among female caffeine users,

Table 11.

Recent Alcohol Use Among Caffeine-Using Participants (N=1560).

EtOH Use Past 30 Days	*% or M (SD)*
Total Sample	----
Number of Days	3.52 (4.81)
Number of Drinks	3.67 (4.46)
Total Quantity	12.22 (27.92)
Males	----
Number of Days	3.95 (5.31)
Number of Drinks	4.56 (6.42)
Total Quantity	15.65 (34.47)
Females	----
Number of Days	3.30 (4.52)
Number of Drinks	3.19 (2.82)
Total Quantity	10.38 (23.48)

Note: Etoh = alcohol.

CWH was most often reported by moderate (25.8%) drinkers and lowest in abstainers (11.3%) ($\chi^2(1) = 18.60$, $p < .001$). For males, no difference was found across the four alcohol groups (Table 12). As shown in Table 17, there was no significant association between alcohol

Table 12.

Alcohol Consumption Patterns by Gender and CWH.

Alcohol Class	*Sample N (%)*	*CWH+ N (%)*	*CWH- N (%)*	χ^2	*df*	*p*
Total Sample (1538)	----	239 (15.5)	1299 (84.5)	14.42	3	.002
Abstainer	555 (36.1)	62 (11.2)	493 (88.8)			
Light Drinker	697 (45.3)	119 (17.1)	578 (82.9)			
Moderate Drinker	252 (16.4)	52 (20.6)	200 (79.4)			
Heavy Drinker	34 (2.2)	6 (17.6)	28 (82.4)			
Males (534)	----	62 (11.6)	472 (88.4)	.185	3	.980
Abstainer	193 (36.1)	21 (10.9)	172 (89.1)			
Light Drinker	233 (43.6)	28 (12.0)	205 (88.0)			
Moderate Drinker	93 (17.4)	11 (11.8)	82 (88.2)			
Heavy Drinker	15 (2.8)	2 (13.3)	13 (86.7)			
Females (1004)	----	177 (17.6)	827 (82.4)	18.60	3	< .001

Abstainer	362 (36.1)	41 (11.3)	321 (88.7)
Light Drinker	464 (46.2)	91 (19.6)	373 (80.4)
Moderate Drinker	159 (15.8)	41 (25.8)	118 (74.2)
Heavy Drinker	19 (1.9)	4 (21.1)	15 (78.9)

frequency in males and CWH (p = .491); however, there was a significant association among females ($\chi^2(1) = 3.81$, p = .051). Further, according to the Wald criterion, the total quantity of alcohol consumed was a significant predictor of CWH in females ($\chi^2(1) = 10.83$, $p < .001$), but not males (p = .832). There was no significant gender association between alcohol quantity and CWH (p = .552 for males; p = .468 for females).

Among participants who reported caffeine use, N = 235 (15.4%) reported alcohol tolerance. Gender specific analyses found that one-third of females with alcohol tolerance (30.1%) reported CWH as compared to 15.5% of those without alcohol tolerance ($\chi 2$ (1) = 17.83, $p < .001$). This relationship was not found in males (p = .659).

Table 13.

Alcohol Tolerance and Peer Alcohol Use by CWH and Gender.

Variables	*Total Sample N (%)*	*CWH+ N (%)*	*CWH- N (%)*	χ^2	*df*	*p*
Alcohol Tolerance – Total (1529)	----	238 (15.6)	1291 (84.4)	12.98	1	< .001
Yes	235 (15.4)	55 (23.4)	180 (76.6)			
No	1294 (84.6)	183 (14.1)	1111 (85.9)			
Alcohol Tolerance – Males (530)	----	62 (11.7)	468 (88.3)	0.19	1	.659
Yes	92 (17.4)	12 (13.0)	80 (87.0)			
No	438 (82.6)	50 (11.4)	388 (88.6)			
Alcohol Tolerance – Females (999)	----	176 (17.6)	823 (82.4)	17.83	1	< .001
Yes	143 (14.3)	43 (30.1)	100 (69.9)			
No	856 (85.7)	133 (15.5)	723 (84.5)			
Peer Problems w/ EtOH – Total (1550)	----	241 (15.5)	1309 (84.5)	40.85	2	< .001
None	619 (39.9)	63 (10.2)	556 (89.8)			
A few or Some	826 (53.3)	143 (17.3)	683 (82.7)			
Most or All	105 (6.8)	35 (33.3)	70 (66.7)			

Peer Problems w/ EtOH – Males (536)	----	62 (11.6)	474 (88.4)	19.53	2	< .001
None	225 (42.0)	11 (4.9)	214 (95.1)			
A few or Some	284 (53.0)	44 (15.5)	240 (84.5)			
Most or All	27 (5.0)	7 (25.9)	20 (74.1)			
Peer Problems w/ EtOH –Females (1014)	----	179 (17.7)	835 (82.3)	23.38	2	< .001
None	394 (38.9)	52 (13.2)	342 (86.8)			
A few or Some	542 (53.5)	99 (18.3)	443 (81.7)			
Most or All	78 (7.7)	28 (35.9)	50 (64.1)			

Note: EtOH = alcohol.

Table 13 presents CWH rates in participants who reported peer problems with alcohol. Over half N = 826 (53.3%) reported "a few or some" of their peers have problems with alcohol; prevalence rates of CHW were highest among those who reported "most or all" of their peers had alcohol problems (33.3%). For both males and females, CWH was highest among those individuals reporting "most or all" of their peers had problems with alcohol (25.9% for males and 35.9% for females) and lowest in those reporting "none" of their peers had problems with alcohol (4.9% for males and 13.2% for females). Chi-square analyses revealed a significant association between peer alcohol problems and CWH for both males and females (see Table 13).

Nicotine

Smoking cigarettes was the most common form of tobacco use, with N = 599 participants (38.4%) reporting ever having smoked a cigarette. Over one-fourth, N = 43 (27.7%) of caffeine users reported smoking 100+ cigarettes in their lifetime (Table 14). Cigar use was most prevalent among males when compared to females (13.7% vs. 5.6%, respectively) as well as hookah use (10.1% vs. 8.4%, respectively) (see Table 15). CWH's were more often reported

Table 14.

Lifetime Cigarette Smoking by CWH and Gender.

Lifetime Cigarette Use	*Total Sample N (%)*	*CWH+ N (%)*	*CWH- N (%)*	χ^2	*df*	*p*
Total (1552)	----	241 (15.5)	1311 (84.5)	27.80	2	< .001
None	953 (61.4)	117 (12.3)	836 (87.7)			
1-99 Cigarettes	444 (28.6)	81 (18.2)	363 (81.8)			
100+ Cigarettes	155 (10.0)	43 (27.7)	112 (72.3)			
Males (537)	----	62 (11.5)	475 (88.5)	17.15	2	< .001
None	302 (56.2)	24 (7.9)	278 (92.1)			
1-99 Cigarettes	164 (30.5)	20 (12.2)	144 (87.8)			
100+ Cigarettes	71 (13.2)	18 (25.4)	53 (74.6)			
Females (1015)	----	179 (17.6)	836 (82.4)	16.85	2	< .001
None	651 (64.1)	93 (14.3)	558 (85.7)			
1-99 Cigarettes	280 (27.6)	61 (21.8)	219 (78.2)			
100+ Cigarettes	84 (8.3)	25 (29.8)	59 (70.2)			

among persons smoking 100+ cigarettes in their lifetime, followed by 1-99 cigarettes and finally no cigarettes. This was true for both males and females. Less than 20% of those who reported caffeine use reported recent (past month) cigarette smoking, with 6% reporting daily smoking. When examined separately by gender, nearly one-third of male daily smokers (29.7%) reported CWH as compared to only 7.3% of non-smokers (p<.001). In contrast, while female rates of CWH also varied across current smoking groups (p<.012), highest rates were found in both daily (26.8%) and multiple day/week (28.2%) smokers, with lowest rates among non-smokers (15.9%). Chi-square analyses revealed a significant relationship between gender and lifetime and monthly cigarette use, and CWH; however, no significant relationship existed between cigar or hookah use and CWH for either gender (Table 15).

Table 15.

Monthly Cigarette, Cigar and Hookah Use by CWH and Gender.

Cigarette Use	*Total Sample N (%)*	*CWH+ N (%)*	*CWH- N (%)*	χ^2	*df*	*p*
Total (1560)	----	241 (15.4)	1319 (84.6)	19.54	3	< .001
None	1254 (80.4)	173 (13.8)	1081 (86.2)			
Once or Twice	88 (5.6)	13 (14.8)	75 (85.2)			
Multiple Days	125 (8.0)	29 (23.2)	96 (76.8)			
Daily	93 (6.0)	26 (28.0)	67 (72.0)			
Males (541)	----	62 (11.5)	479 (88.5)	15.80	3	.001
None	409 (75.6)	39 (9.5)	370 (90.5)			
Once or Twice	41 (7.6)	3 (7.3)	38 (92.7)			
Multiple Days	54 (10.0)	9 (16.7)	45 (83.3)			
Daily	37 (6.8)	11 (29.7)	26 (70.3)			
Females (1019)	----	179 (17.6)	840 (82.4)	10.95	3	.012
None	845 (82.9)	134 (15.9)	711 (84.1)			
Once or Twice	47 (4.6)	10 (21.3)	37 (78.7)			
Multiple Days	71 (7.0)	20 (28.2)	51 (71.8)			
Daily	56 (5.5)	15 (26.8)	41 (73.2)			

Cigar Use	*Total Sample N (%)*	*CWH+ N (%)*	*CWH- N (%)*	χ^2	*df*	*p*
Total (1544)	----	239 (15.5)	1305 (84.5)	0.23	2	.890
None	1221 (79.1)	187 (15.3)	1034 (84.7)			
Once or Twice	193 (12.5)	30 (15.5)	163 (84.5)			
Multiple Days	130 (8.4)	22 (16.9)	108 (83.1)			
Males (534)	----	62 (11.6)	472 (88.4)	0.05	2	.975
None	376 (70.4)	43 (11.4)	333 (88.6)			
Once or Twice	85 (15.9)	10 (11.8)	75 (88.2)			
Multiple Days	73 (13.7)	9 (12.3)	64 (87.7)			
Females (1010)	----	177 (17.5)	833 (82.5)	1.21	2	.519
None	845 (83.7)	144 (17.0)	701 (83.0)			
Once or Twice	108 (10.7)	20 (18.5)	88 (81.5)			
Multiple Days	57 (5.6)	13 (22.8)	44 (77.2)			

Hookah Use	*Total Sample N (%)*	*CWH+ N (%)*	*CWH- N (%)*	χ^2	*df*	*p*
Total (1543)	----	239 (15.5)	1304 (84.5)	1.25	2	.535
None	1115 (72.3)	168 (15.1)	947 (84.9)			

Once or Twice	289 (18.7)	45 (15.6)	244 (84.4)			
Multiple Days	139 (9.0)	26 (18.7)	113 (81.3)			
Males (533)	----	62 (11.6)	471 (88.4)	0.83	2	.661
None	378 (70.9)	44 (11.6)	334 (88.4)			
Once or Twice	101 (18.9)	10 (9.9)	91 (90.1)			
Multiple Days	54 (10.1)	8 (14.8)	46 (85.2)			
Females (1010)	----	177 (17.5)	833 (82.5)	1.19	2	.552
None	737 (73.0)	124 (16.8)	613 (83.2)			
Once or Twice	188 (18.6)	35 (18.6)	153 (81.4)			
Multiple Days	85 (8.4)	18 (21.2)	67 (78.8)			

As summarized in Table 16, rates of CWH varied across peer smoking groups, with similar patterns in males and females. Specifically, highest rates of CWH were reported by participants with most/all peers described as smokers and lowest rates of CWH were found in those with largely non-smoking peers (all p<.001).

Table 16.

Peer Cigarette Use by CWH and Gender.

Variables	*Total Sample N (%)*	*CWH+ N (%)*	*CWH- N (%)*	χ^2	*df*	*p*
Peer Cigarette Use – Total (1556)	----	241 (15.5)	1315 (84.5)	30.24	2	< .001
None	435 (28.0)	45 (10.3)	390 (89.7)			
A Few or Some	910 (58.5)	139 (15.3)	771 (84.7)			
Most or All	211 (13.6)	57 (27.0)	154 (73.0)			
Peer Cigarette Use – Males (538)	----	62 (11.5)	476 (88.5)	17.65	2	< .001
None	115 (21.4)	6 (5.2)	109 (94.8)			
A Few or Some	340 (63.2)	36 (10.6)	304 (89.4)			
Most or All	83 (15.4)	20 (24.1)	63 (75.9)	.		
Peer Cigarette Use – Females (1018)	----	179 (17.6)	839 (82.4)	17.85	2	< .001
None	320 (31.4)	39 (12.2)	281 (87.8)			
A Few or Some	570 (56.0)	103 (18.1)	467 (81.9)			
Most or All	128 (12.6)	37 (28.9)	91 (71.1)			

Psychopathology, Personality, and Parental History

Mood and personality scale ratings for participants with and without a history of CWH are summarized in Table 17. According to the Wald criterion, the participant's self-reported depression ($\chi^2(1) = 20.02$, $p < .001$) and anxiety ($\chi^2(1) = 23.49$, $p < .001$) symptoms were significant predictors of CWH. Further, the personality factor openness ($\chi^2(1) = 6.76$, $p = .009$) was associated with CWH, where the change in odds associated with a one-unit change in a participant's openness score was 1.03, indicating that a one-unit change resulted in the participant having a 1.06 times greater likelihood to experience CWH. The personality factor neuroticism was also found to be a significant predictor of CWH ($\chi^2(1) = 24.94$, $p < .001$). By comparison, the probability of CWH increases as agreeableness (OR = 0.96) decreases ($p = .002$).

Table 17.

Univariable Regression Analyses for Each Continuous Psychosocial Variable and their Relationship to Caffeine withdrawal (N = 1560).

Variables	*B*	*S.E.*	*Wald*	*df*	*p*	*Odds Ratio*	*95% C.I. for Ex(B)*	
							Lower	*Upper*
Alcohol								
Alcohol Frequency	.029	.016	3.17	1	.075	1.03	0.99	1.06
Males	.020	.029	.474	1	.491	1.02	0.96	1.01
Females	.039	.020	3.81	1	.051	1.04	1.00	1.08
Alcohol Quantity	-.011	.025	0.18	1	.668	0.99	0.94	1.04
Males	-.029	.049	.353	1	.552	0.97	0.88	1.07
Females	.028	.039	.527	1	.468	1.03	0.95	1.11
Total Alcohol Consumed	.005	.002	4.66	1	.031	1.01	1.00	1.01
Males	-.001	.005	.045	1	.832	1.00	0.99	1.01
Females	.012	.003	10.829	1	.001	1.01	1.01	1.02
Mood - Depression								
Total	.398	.089	20.02	1	< .001	1.49	1.25	1.77
Male	.400	.183	4.769	1	.029	1.49	1.04	2.13
Female	.353	.104	11.64	1	.001	1.42	1.16	1.74
Mood - Anxiety								
Total	.449	.093	23.49	1	<	1.57	1.31	1.88

					.001			
Males	.547	.208	6.88	1	.009	1.73	1.15	2.60
Females	.374	.105	12.62	1	< .001	1.45	1.18	1.79
Personality Factors								
Extraversion								
Total	.013	.011	1.34	1	.248	1.01	0.99	1.04
Males	-.028	.021	1.81	1	.178	0.97	0.93	1.01
Females	.026	.013	3.70	1	.055	1.03	1.00	1.05
Agreeableness								
Total	-.037	.012	9.46	1	.002	0.96	0.94	0.99
Males	-.076	.024	10.19	1	.001	0.93	0.88	0.97
Females	-.029	.014	4.24	1	.040	0.97	0.94	1.00
Conscientiousness								
Total	-.014	.012	1.23	1	.267	0.99	0.96	1.01
Males	-.042	.024	3.03	1	.082	0.96	0.92	1.01
Females	-.007	.014	0.26	1	.612	0.99	0.97	1.02
Neuroticism								
Total	.057	.011	24.94	1	< .001	1.06	1.04	1.08
Males	.074	.023	10.30	1	.001	1.08	1.03	1.13
Females	.042	.014	9.48	1	.002	1.04	1.02	1.07
Openness								
Total	.033	.013	6.76	1	.009	1.03	1.01	1.06
Males	.044	.025	2.99	1	.084	1.05	0.99	1.10
Females	.032	.014	4.93	1	.026	1.03	1.00	1.06

Table 18 summarizes the results of chi-square analyses examining the relationship between CWH and self-report of parental problems with alcohol, drugs, and/or anxiety/depression. For the entire sample as well as both males and females, prevalence rates were highest for maternal depression or anxiety, with almost one-half (46.5) of the sample reporting maternal depression or anxiety, and 40.8% of males and 49.7% of females reporting the same. Prevalence rates for CWH were highest among females reporting maternal alcohol use (27.7%), maternal drug use (24.6%), and paternal depression or anxiety (24.6%), and lowest among those reporting paternal drug use (18.9%). In males, CWH was highest among those reporting maternal alcohol use (25.6%) and lowest among those reporting paternal drug use (11.6%). There were a number of significant relationships between parental alcohol use, drug use, and anxiety/depression and CHW, with the most significant relationships found between

CWH and maternal alcohol use ($p < .001$) and maternal depression or anxiety ($p < .001$) (see Table 18).

Table 18.

Variables (N)	*Total Sample N (%)*	*CWH+ N (%)*	*CWH- N (%)*	χ^2	*df*	*p*
Family History – (Total Sample)						
Maternal Alcohol Use (1489)	----	229 (15.4)	1260 (84.6)	16.43	1	< .001
Yes	140 (9.4)	38 (27.1)	102 (72.9)			
No	1349 (90.6)	191 (14.2)	1158 (85.8)			
Maternal Drug Use (1489)	----	228 (15.3)	1261 (84.7)	5.01	1	.025
Yes	89 (6.0)	21 (23.6)	68 (76.4)			
No	1400 (94.0)	207 (14.8)	1193 (85.2)			
Maternal Depression or Anxiety (1384)	----	215 (15.5)	1169 (84.5)	22.60	1	< .001
Yes	644 (46.5)	132 (20.5)	512 (79.5)			
No	740 (53.5)	83 (11.2)	657 (56.2)			
Paternal Alcohol Use (1408)	----	218 (15.5)	1190 (84.5)	8.58	1	.003
Yes	342 (24.3)	70 (20.5)	272 (79.5)			
No	1066 (75.7)	148 (13.9)	918 (86.1)			
Paternal Drug Use (1398)	----	209 (14.9)	1189 (85.1)	0.48	1	.489
Yes	212 (15.2)	35 (16.5)	177 (83.5)			
No	1186 (84.8)	174 (14.7)	1012 (85.3)			
Paternal Depression or Anxiety (1282)	----	207 (16.1)	1075 (83.9)	10.25	1	.001
Yes	405 (31.6)	85 (21.0)	320 (79.0)			
No	877 (68.4)	122 (13.9)	755 (86.1)			
Family History – (Males)						
Maternal Alcohol Use (516)	----	59 (11.4)	457 (88.6)	8.41	1	.004
Yes	39 (7.6)	10 (25.6)	29 (74.4)			
No	477 (92.4)	49 (10.3)	428 (89.7)			
Maternal Drug Use (514)	----	59 (11.5)	455 (88.5)	2.17	1	.141
Yes	24 (4.7)	5 (20.8)	19 (79.2)			
No	490 (95.3)	54 (11.0)	436 (89.0)			
Maternal Depression or Anxiety (488)	----	56 (11.5)	432 (88.5)	10.41	1	.001
Yes	199 (40.8)	34 (17.1)	165 (82.9)			
No	289 (59.2)	22 (7.6)	267 (92.4)			
Paternal Alcohol Use (498)	----	56 (11.2)	442 (88.8)	1.88	1	.171
Yes	107 (21.5)	16 (15.0)	91 (85.0)			
No	391 (78.5)	40 (10.2)	351 (89.8)			
Paternal Drug Use (498)	----	54 (10.8)	444 (89.2)	0.05	1	.829
Yes	69 (13.9)	8 (11.6)	61 (88.4)			

No	429 (86.1)	46 (10.7)	383 (89.3)			
Paternal Depression or Anxiety (463)	----	54 (11.7)	409 (88.3)	0.40	1	.528
Yes	129 (27.9)	17 (13.2)	112 (86.8)			
No	334 (72.1)	37 (11.1)	297 (88.9)			
Family History – (Females)						
Maternal Alcohol Use (973)	----	170 (17.5)	803 (82.5)	8.21	1	.004
Yes	101 (10.4)	28 (27.7)	73 (72.3)			
No	872 (89.6)	142 (16.3)	730 (83.7)			
Maternal Drug Use (975)	----	169 (17.3)	806 (82.7)	2.58	1	.108
Yes	65 (6.7)	16 (24.6)	49 (75.4)			
No	910 (93.3)	153 (16.8)	757 (83.2)			
Maternal Depression or Anxiety (896)	----	159 (17.7)	737 (82.3)	11.08	1	.001
Yes	445 (49.7)	98 (22.0)	347 (78.0)			
No	451 (50.3)	61 (13.5)	390 (86.5)			
Paternal Alcohol Use (910)	----	162 (17.8)	748 (82.2)	5.80	1	.016
Yes	235 (25.8)	54 (23.0)	181 (77.0)			
No	675 (74.2)	108 (16.0)	567 (84.0)			
Paternal Drug Use (900)	----	155 (17.2)	745 (82.8)	0.33	1	.567
Yes	143 (15.9)	27 (18.9)	116 (81.1)			
No	757 (84.1)	128 (16.9)	629 (83.1)			
Paternal Depression or Anxiety (819)	----	153 (18.7)	666 (81.3)	9.72	1	.002
Yes	276 (33.7)	68 (24.6)	208 (75.4)			
No	543 (66.3)	85 (15.7)	458 (84.3)			

Multivariable Regression Analysis:

Direct logistic regression was employed to predict CWH, with a pool of 15 variables identified through univariable analyses. They included: gender (male/female); race (white/non-white); daily caffeine use (y/n); alcohol tolerance (y/n); current daily cigarette smoking (y/n); peers problem with drinking (y = "most or all"/no); peer cigarette use (y = "most or all"/no); self-reported depression and anxiety (continuous variable); the personality factors of neuroticism and openness (continuous variables); maternal depression or anxiety (y/n); maternal alcohol use (y/n); paternal depression or anxiety (y/n), and paternal alcohol use (y/n).

A test of the full model against a constant-only model was significant, $\chi^2(15) = 156.53$, $p < .001$, indicating that as a set, the predictors distinguished between those with and without

CWH better than an intercept alone model. The final parsimonious model was significant ($\chi^2(6) = 149.91$, $p < .001$) and accounted for approximately 23% of the variance. This model included: gender ($\chi^2(1) = 5.41$, $p = .020$); race ($\chi^2(1) = 22.66$, $p < .001$); daily caffeine use ($\chi^2(1) = 51.65$, $p < .001$); peer problems with alcohol ($\chi^2(1) = 8.59$, $p = .003$); the personality factor neuroticism ($\chi^2(1) = 7.60$, $p = .006$), and maternal depression or anxiety ($\chi^2(1) = 6.13$, $p = .013$).

Accurate classification of cases from all 6 predictors was high for the prediction of not experiencing CWH (98.2%) but poor for the prediction of CWH (10.4%), for an overall success rate of 84.6%. Thus while these variables reliably distinguished between participants experiencing CWH vs. not experiencing CWH, the distinction is not strong.

Table 19.

Prediction of CWH using a Multivariable Regression Analysis.

Variables	*B*	*S.E.*	*Wald*	*df*	*p*	*Odds Ratio*	*95% C.I. for Ex(B)*	
							Lower	*Upper*
Gender	.486	.209	5.41	1	.020	1.63	1.08	2.45
Race	1.02	.215	22.66	1	< .001	2.78	1.82	4.23
Daily Caffeine Use	1.30	.181	51.65	1	< .001	3.66	2.57	5.22
Peer Problems with Alcohol	.828	.283	8.59	1	.003	2.29	1.32	3.98
Neuroticism	.041	.015	7.60	1	.006	1.04	1.01	1.07
Maternal Depression or Anxiety	.461	.186	6.13	1	.013	1.59	1.10	2.28

As shown in Table 19, the odds ratios ranged from 1.04 (CI = 1.01 – 1.07) for neuroticism to 3.66 (CI = 2.57 – 5.22) for daily caffeine use. Taken together, the probability of experiencing CWH significantly increased for females and for non-white minority group members; the probability of experiencing CWH also significantly increased for those who were daily users (7 days/week) of any caffeine product, reported peer problems with alcohol, scored

high in neuroticism, and reported that their biological mother had problems with depression or anxiety.

Discussion

Caffeine is remarkable in that it is a behaviorally active drug that is widely and regularly consumed by individuals of nearly all ages. Despite the estimated use and prevalence of caffeine, and its well-documented pharmacological effects, no validated measure to accurately quantify caffeine use exists to date. Furthermore, caffeine is a drug that is subject to symptoms consistent with problematic use, including tolerance and withdrawal. However, only recently has caffeine withdrawal been recognized in the Diagnostic and Statistical Manual-5 (DSM-5) (APA, 2013), and to date there has been little research on individual differences in the experience of caffeine withdrawal. Since heavy caffeine use increases risk for many adverse consequences, it is important that we understand consumption patterns and their relationship to caffeine withdrawal.

The present study examined caffeine consumption patterns and the experience of caffeine withdrawal in a freshman sample of males and females from the VCU Spit for Science project. The present study also identified demographic and psychosocial variables associated with having CWH's and determined which of these variables, in combination with caffeine use measures, best predicted caffeine withdrawal-headache. This is the first study to examine demographic and psychosocial variables associated with CWH in a college sample of males and females.

Summary of Findings

Approximately 80% of young adults reported caffeine use, which was similar to, or slightly lower than, other national estimates (Fulgoni et al., 2015), and caffeine withdrawal headache was the most frequently reported symptom. Females were more likely than males to

consume caffeine, but sodas were the main source of caffeine for both genders. Likelihood of experiencing a CWH varied by consumption patterns, beverage type, and gender. Overall, daily caffeine consumers were more likely to report CWH than non-daily caffeine consumers, with daily coffee drinking females reporting the highest rates of CWH.

In univariable analyses, associations were found between a number of psychosocial variables and CWH. Alcohol consumption and peer alcohol use were positively associated with CWH, with highest rates of CWH found in females reporting problems with alcohol. For tobacco use, male daily cigarette smokers were more likely to report CWH when compared to females, while female rates of CWH varied across all smoking groups. Further, rates of CWH varied across peer smoking groups, with the highest rates of CWH being reported by participants with most/all peers described as smokers and lowest rates were found in those with largely non-smoking peers. Similar patterns were found in males and females. Both male and female participants reporting maternal depression/anxiety or alcohol problems displayed significant associations with CWH. Positive associations were also found between self-reported depression and anxiety and CWH. When personality measures were tested, openness and neuroticism predicted CWH, but agreeableness did not.

The variables found significant ($p<.25$) through univariable analyses were entered into a multiple backward stepwise regression analysis. Overall, the probability of experiencing CWH significantly increased for females and non-white minority group members, and for those who were daily users (7 days/week) of any caffeine product, reported peer problems with alcohol, scored high in neuroticism, and reported that their biological mother had problems with depression or anxiety.

Discussion of Findings

Caffeine consumption among college students. In the present study, eighty percent of the college freshman reported recent caffeine use. Other studies examining patterns of caffeine use in college samples have come to similar conclusions. For example, Norton and colleagues (2011) found that overall, 89% of their sample (n = 685; mean age 18.89 years) reported caffeine use in the past 30 days, with an average daily consumption of 196 mg/day. Of those reporting any caffeine consumption, 81% reported consumption in soft drinks, 42% in energy drinks and shots, 41% in coffee, 29% in tea, and 14% in espresso and lattes. In addition, recent work among first-year college students suggests that 65% of students drink caffeinated beverages on a daily basis, and 94.7% of students used some form of caffeine in the last 2 weeks (McIlvain, Noland, & Bickel, 2011).

While our overall caffeine consumption rates compare to these studies, our beverage use patterns vary considerably, especially regarding energy drinks. For example, the findings noted by Norton and colleagues (2011) are considerably different from our findings, which reported only 16% of caffeine consumers use energy drinks, with only 0.7% of consumers using energy drinks daily. These inconsistencies are likely due to differences in age, however. Caffeine intake has been positively associated with age in most studies (Ahluwalia & Herrick, 2015) and Norton et al. (2011) included participants from all grades, with an age range from 16-30, and found that older participants and upperclassmen reported higher levels of caffeine consumption in a typical week, with age and year in school being highly correlated.

Because of the growing popularity of energy drinks, the increase in associated risks with energy drink consumption among college students (Arria & O-Brien, 2011), and markets for the energy drink industry aggressively targeting adolescents and young adults aged 18–34 years

(Heckman et al., 2010), the vast majority of studies estimating caffeine consumption patterns among this population focuses on energy drink use. For instance, a study conducted by Poulos and Pasch (2016) found that approximately 56% of first-year college students consumed energy drinks, with 65% of these students consuming energy drinks in the past month and 38.5% consuming energy drinks in the past week. However, even though Poulos and Pasch's (2016) past-month energy drink consumption patterns corroborate with previous research (e.g., Arria et al., 2011), their past week consumption is almost double compared to Arria and colleagues (2011) (19.8%). Poulos and Pasch (2016) note that these differences may be due to the timing of the survey. For example, their survey was conducted towards the end of the spring semester, which covered the final exam period, whilst Arria and colleagues (2011) assessed their participants at some point during their academic year. Because of caffeine's physiological and psychological effects, students may have consumed more recent energy drinks than is typical due to the increased stress of studying for exams. These differences in survey timing could also account for the low energy drink consumption found in the present study.

It should also be noted that interestingly, both Poulos and Pasch (2016), using first-year college students (n = 585), and Arria et al. (2011), using fourth-year college students (n = 1253), found approximately 56-61% of their sample consumed energy drinks. This is almost 4 times the amount found in the present study. However, both Poulos and Pasch (2016) Arria and colleagues (2014) stratified their data analyses according to past year energy drink consumption versus past month energy drink consumption assessed in the present study.

Moreover, previous research conducted by Malinauskas and colleagues (2007) estimated that 51% percent of their college sample (mean age of 21.5 years; n = 496) consumed greater than one energy drink each month in an average month. Pettit and DeBarr (2011), who surveyed

136 undergraduate students (aged 18 to 24 years), found that more than half (59.1%) of participants consumed an energy drink on at least 1 of the past 7 days, and found 70.1% of participants consumed at least 1 energy drink during the past 30 days. Research conducted by Velazquez et al., 2012) reported that among 585 undergraduate students (mean age = 18.7 years), nearly 40% of students reported consuming energy drinks in the past month and 17.5% of students reported consuming energy drinks in the past week.

Interestingly, our energy drink consumption rates most closely matched that of Berger, Fendrick, Chen, Arria, and Cisler (2011), who assessed a large community sample (n = 946, aged 18 to 92 years) and found that close to one-fourth of respondents consumed at least one energy drink in the past year. This estimate is lower than what is reported in studies of college students (38 to 51%) (Malinauskas et al., 2007; Miller, 2008a; Miller, 2008b) most likely because of the broad age range analyzed; however, the author's note that that energy drink users were more likely to be younger (Berger et al., 2011).

The above differences in energy drink consumption patterns must be interpreted in light of several possible reasons, especially when comparing the results to the present study. First, like mentioned above, many of the differences could be attributable to the timing of the surveys. First- year students were able to participate in the present study at any point in the semester, while Poulos and Pasch (2016) and Velazquez et al. (2012) assessed their participants at the end of their first year in college. Second, each of the studies are self-report studies, which are always subject to response bias, such as over- or under-reporting. Third, many of the above studies ascertained young adults from one large public university in various U.S. locations, and because students' consumption patterns may be associated with changes in their environment, the influences of different social situations may account for differences in caffeine consumption.

Lastly, with widely varying caffeine content both within and across beverage types and minimal standardization (Irons, Bassett, Prendergast, Landrum, & Heinz, 2016), young adults have shown surprisingly little knowledge surrounding energy drinks. For example, some students have been found to be unfamiliar with many of the common energy drink ingredients and/or their potential side effects, in addition to being unable to distinguish energy drinks from sports drinks (Attila & Çakir, 2011). These inconsistencies in caffeine reporting suggest a potential knowledge gap regarding what exactly constitutes an energy drink. This lack of knowledge could result in survey reporting errors, and such reporting errors can weaken accurate assessments of use.

Gender differences in caffeine consumption. The present study found that overall, females (65.3%) were more likely to use caffeine than males (34.7%), and they were more likely to drink coffee, tea, soda, and other caffeinated beverages; females were also more likely to report use of caffeinated medicines than males. Males, however, were more likely than females to consume energy drinks. In addition, we found that among daily caffeine consumers, males consumed coffee and soda more than females, while females consumed more tea. There was an equal percentage of daily energy drink consumption for both genders, although like mentioned above, the percentage was very low. In terms sample representation, our sample has a disproportionate amount of females represented compared to males (61% were female).

In general, research examining gender differences in caffeine consumption patterns has been mixed. In healthy and clinical samples, men generally consume more caffeine than women (Ciapparelli et al., 2010; Lee, McEnany, & Weekes, 1999; Waldeck & Miller, 1997). Also, a study conducted by Demura et al., (2013) found that among 1189 young people (567 males aged 19.3 ± 1.5 years; 622 females aged 19.1 ± 1.2 years, coffee use was significantly higher in males (50.8%) than in females (32.8%). However, other studies have examined caffeine use students

and in the general population and found consumption did not vary as a function of gender (Brice & Smith, 2002; Jones & Lejuez, 2005; Whalen et al., 2007). Other studies examining energy drink use among college students found that men were more likely to consume energy drinks when compared to women (Arria, Caldeira, Kasperski, et al., 2010; Arria et al., 2011; Berger et al., 2011; Hoyte, et al., 2013; Miller, 2008a, 2008b; Nordt et al., 2012; O'Brien, McCoy, Rhodes Wagoner, & Wolfson, 2008; Pettit & DeBarr, 2011; Velazquez et al., 2012). However, Lieberman et al., (2015) found in a sample of college students that caffeine intake was higher among women, and Malinauskas and colleagues (2007), also in a sample of college students, found that women were more likely to consume energy drinks when compared to men.

Despite demographic comparisons, many studies do not examine reasons why gender specific differences exist. Some researchers suspect gender differences exist because of circulating hormones (Temple & Ziegler, 2011) and other physiological differences (Harley, Lavallo, & Whitsett, 2004; Lovallo, Farag, Vincent, Thomas, & Wilson, 2006; Keogh & Witt, 2003; Temple et al., 2014). Furthermore, according to Yamazawa, Hirokawa, and Shimizu (2007) gender differences in preferences for sweet coffee were related to coffee drinking habits in a sample of undergraduate students. In addition, Adan, Prat, Fabbri, and Sànchez-Turet, (2008), found that caffeine at lower doses induced greater effects in undergraduate men (less somnolence and greater activation) than in women, suggesting that females may need to consume more caffeine to experience caffeine's physiological effects. Further, Claire, Hayward, and Rogers (2010) found that female undergraduate students performed much better on collaborative tasks under stress when compared to males.

Like the present study, which had a higher number of females compare to males, the studies conducted by Arria et al., (2011), O'Brien and colleagues (2008), and Pettit and DeBarr

(2011) had higher survey response rates in females when compared to males, but all three studies found males to consume more energy drinks, similar to the present study. These findings are consistent with reported marketing practices that target young adults, and in particular, males through the sponsorship of male-dominated extreme sports (e.g., motocross) (Reissig et al., 2009; Simon and Mosher, 2007).

National prevalence rates and beverage intake patterns. The rate of caffeine consumption found in the present study is also comparable to those found in national and more diverse samples (Ahluwalia et al., 2014; Branum et al., 2014; Fulgoni, 2014; Fulgoni et al., 2015; Mitchell et al., 2014); although, these studies have come from samples examining caffeine consumption data over varying study periods (e.g., 1999–2010 (Branum et al., 2014), 2001–2010 (Ahluwalia et al., 2014; Fulgoni et al., 2015)) and in broad age ranges including opposite ends of the age spectrum from young children to older adults. Additionally, these studies examined dietary data from a single day (Ahluwalia et al., 2014; Branum et al., 2014; Fulgoni et al., 2015), 2-day (Fulgoni, 2014), and 7-day (Mitchell et al., 2014); they also did not include intakes from medicines (e.g., diet pills, antidrowsiness pills), and Mitchell et al. (2014) was the only study to report on supplements such as energy shots. However, regardless of the methodological differences in data collection and/or data analysis, the results of the present study provide good evidence for the overall relative stability of caffeine consumption from beverages in the U.S. (Mitchell et al., 2014).

For beverages, we found that prevalence rates varied with two-thirds of the sample drinking sodas (65.7%), followed by tea (54.2%) and coffee (51.6%). Prevalence of energy drink and/or shot use was lower (16% and 4%, respectively). Our findings compare to Fulgoni and colleagues (2015) who found that coffee (64%), tea (16%), and soft drinks (18%) to be

predominant sources of caffeine among those ≥ 19 years old; however, our percentage rates substantially differed. Additionally, our findings corroborate with other studies (Ahluwalia & Herrick, 2015; Branum et al., 2014; Fulgoni (2014); Mitchell et al., 2014) where among caffeine consumers, soda, tea, and coffee were the major sources of caffeine among all age groups examined (2-59 years). Contrary to our findings, however, Drewnowski and Rehm (2016), based on the NHANES data, reported a decline in caffeine from soda over the past 14 years, noting that coffee and tea represent a greater proportion of caffeine intakes across all age groups.

Caffeine Withdrawal. The present study found that approximately one-fifth of the sample of caffeine users reported symptoms of caffeine withdrawal (20.4%; n = 319). Headaches were most prevalent (15.4%), followed by fatigue, anxiety, depression, and nausea/vomiting. Females more likely than males to report headaches, fatigue, and to report one or more symptoms of caffeine withdrawal when compared to males. Further, three-fourths of the subgroup reporting CWH were female.

Most research on caffeine withdrawal has examined symptoms in adults (Julian & Griffiths, 2004), however, there have been a few empirical studies demonstrating that young adults (e.g., college students) also experience caffeine withdrawal. In 2012, Anderson and Juliano found that among college students (n = 225; 81.8% female), 32.8% indicated having had experienced caffeine withdrawal symptoms. Another study, which surveyed 300 freshmen (60.7% women) attending a southeastern university, found that 51% reported having at least one sign/symptom of caffeine withdrawal. The most common symptoms of withdrawal were fatigue (20%), headache (36%) and cravings (25%), and the experience of caffeine withdrawal headaches did not significantly differ by gender (McIlvain et al., 2011).

Additionally, Malinauskas and colleagues (2007), found that among energy drink consumers (*n* = 253; 53% female), 22% reported ever having headaches and 19% reporting experiencing heart palpitations. Another study, conducted by Jones and Lejuez (2005), found that among 60 caffeine consuming college students (50% female), 73% reported experiencing withdrawal; however, their inclusion criteria included only students who fulfilled *DSM-IV* diagnosis of Substance Dependence as applied to caffeine based on a modified version of the Module E of the Structured Clinical Interview for *DSM-IV* Axis 1 Disorders – Non-Patient Edition (SCID-NP). This type of semistructured interview procedure is also vastly different from self-report surveys.

Findings from the present study yield conflicting results. One possible explanation is that there are substantial differences within and across individuals with regard to incidence of caffeine withdrawal. For example, approximately 50% of regular caffeine users report headache by the end of the first day of abstinence (Juliano & Griffiths, 2004); however, in experimental studies investigating caffeine withdrawal, one study examining repeated abstinence trials showed distinct differences within and across subjects: one individual never showed CWH, some showed consistent headaches, and others reported headaches on some trials but not on other trials (Griffiths et al., 1990). Moreover, in another repeated abstinence experimental study, approximately 36% of the subjects who displayed significant elevations in headaches failed to report this effect consistently across trials (Hughes et al., 1993).

Furthermore, caffeine may have varying effects from one person to the next due to differing age, lifestyle, or personality (Brice & Smith, 2002), and the severity of signs or symptoms of caffeine withdrawal can vary from mild to extreme (Juliano & Griffiths, 2004). Relatively low doses of caffeine (e.g. as little as 25 mg) can also partially suppress withdrawal

symptoms. Thus, some people may fail to report withdrawal because they unknowingly consumed small amounts of caffeine on days they thought they were abstinent of caffeine. Additionally, many caffeine consumers may be unaware of their physical dependence on caffeine because their frequent habitual consumption precludes a period of sustained abstinence (e.g. 2 days). Lastly, participants may have attributed their caffeine withdrawal symptoms to other causes or ailments (e.g., viral infection), or they did not believe their symptoms to be incapacitating enough to report.

Another possible explanation is regarding the persistent methodological challenges in caffeine research. For example, the present study included a screening question, "Do you drink any caffeinated beverages?" If a participant answered "No" to this question, they would skip any subsequent questions asking about caffeine use, including the question asking about the frequency of use of over-the-counter medications (e.g., Vivarin, NoDoz, Excedrin, Vanquish, Anacin, Dristan). Therefore, the present study could have excluded participants who only used over-the-counter caffeinated medicines. Moreover, and similar to Dews et al., (1999), our survey was not solely focused on caffeine withdrawal symptoms, which could have attributed to the low frequency of symptoms not found in previous reports. In addition, Anderson & Juliano (2012), asked their participants, "Have you ever had caffeine withdrawal symptoms or bad physical or emotional feelings after not having caffeine at a time when you usually have it?'' (p. 40). If participants do not have an understanding of the characteristics of caffeine withdrawal, or if a withdrawal symptom is broadly defined, there becomes a potential increased risk for discrepant/inconsistent reporting that could influence results.

The caffeine withdrawal syndrome has been well-characterized in numerous rigorous double-blind studies (Juliano & Griffiths, 2004). Despite the lower rates found in the present

study, our results extents the research on the prevalence of caffeine withdrawal, especially the absent data on gender differences in the experience of caffeine withdrawal. Future research on the prevalence of caffeine withdrawal should continue given the potential for caffeine withdrawal to cause clinically significant distress or impairment in functioning as reflected by the inclusion of caffeine withdrawal in the Diagnostic and Statistical Manual-5 (DSM-5) (APA, 2013).

Psychosocial factors predicting caffeine withdrawal headache. Although there are considerable differences within and across individuals regarding the incidence and/or severity of caffeine withdrawal (Evans & Griffith, 1999; Hughes et al., 1993; Juliano & Griffiths, 2004), to our knowledge only one study has investigated predisposing determinants of caffeine withdrawal. This was lab-based study including the general population, and scientists found no predictors of caffeine withdrawal. The study, however, had only a homogenous sample of only 40 participants, and a limited range of predictor variables (e.g., age, sex, weight, average caffeine intake, duration of caffeine use, smoking status, etc.) (Hughes et al., 1993). Another study, conducted by Evans and Griffiths (1999), did not specifically examine predictors of caffeine withdrawal; however, they did investigate specific dosing conditions under which withdrawal symptoms occur, suggesting that withdrawal can occur under more modest conditions (i.e., fewer doses per day, lower daily dose, and shorter duration of exposure). Despite the present study not looking at quantity consumed, the incidence of caffeine withdrawal found in the literature (Evans & Griffiths, 1999; Juliano & Griffiths, 2004) supports our hypothesis that daily caffeine users would be more likely to experience CWH than non-daily users.

The probability of experiencing CWH also significantly increased for those who reported peer problems with alcohol. To our knowledge, there has been no prior investigation exploring

this relationship. There are possible anecdotal explanations for why this relationship exists, however. First, there has been growing evidence supporting the positive correlation between caffeine consumption, namely energy drink consumption, and alcohol use among young adults and college students (Arria et al., 2011; Anderson & Juliano, 2012; Caldeira et al., 2009; Knight et al., 2002; Velazquez et al., 2012; Wu et al., 2007). If an individual is wanting to refrain from drinking alcohol, an alternate beverage of choice could be caffeine, in particular, energy drinks or caffeinated sodas. Since the social norm may be encouraging overconsumption to the point of intoxication, some individuals may intentionally seek some of the negative effects of caffeine (Ahluwalia & Herrick, 2015). These adverse effects, which may be intentionally sought by high-dose consumers, may be a manifestation of stimulation-seeking behavior (Terry-McElrath et al., 2014). This type of behavior is often seen in young males; however, most individuals, including young males, choose to use moderate doses of caffeine and have characteristic and regular patterns of consumption (Fulgoni et al., 2015, Mitchell et al., 2014).

Another potential reason is to consider the aggressive marketing of energy drinks to youthful and inexperienced consumers (Byerley, 2016). Even though energy drink consumption was relatively low in our sample, the promotion of the use of caffeine for its recreational and stimulant properties sends a potentially harmful message to young adults that glamorizes and encourages its use. Further, with the variable and sometimes very high caffeine content of energy drinks and lack of full disclosure of the amount of caffeine and other ingredients in energy drinks on the product labeling, individuals may be unaware of adverse consequences of caffeine consumption, and thus become more prone to withdrawal (Reissig et al., 2009). The advertised rapid onset of stimulant behavior provided by energy drinks and other caffeinated

beverages may be what drives the use of these beverages in alcohol-related situations, even if one is abstaining from alcohol.

An additional primary finding of the present study was that females were more likely to experience CWH when compare to males. First, it must be noted that females were more likely to use caffeine than males, which could be the principal reason why more females reported CWH when compared to males. However, as mentioned above, some epidemiology studies have concluded that females consume more caffeine than males. Further, with the growing evidence supporting caffeine use in social settings among college students (Lieberman et al., 2015; Malinauskas et al., 2007; Norton et al., 2011), the results of the current study could suggest that females are participating in number of social activities, although this was not specifically investigated. Results of previous studies support the idea that females metabolize caffeine 20% to 30% faster than males (Franconi et al., 2003) and with research suggesting that responses to caffeine differ by gender due to differences in steroid hormone concentrations (Temple & Ziegler, 2011), suggesting an increased susceptibility to caffeine withdrawal. Additionally, our findings corroborate with Kendler and Prescott (1999), who found that genetic factors substantially influence a woman's vulnerability to caffeine use and withdrawal. Nevertheless, reasons for gender differences in caffeine use and dependence are not yet clear and further research regarding pharmacodynamics, pharmacodynamics, and psychosocial factors is warranted. Further, as suggested by the National Institute of Health, analyzing data by sex/gender at all levels of analysis in both animal and human studies will provide valuable insight into these gender differences.

Another intriguing finding from the present study is that the probability of experiencing CWH increased significantly for participants of the non-white minority group. Few studies have

examined patterns and reasons for consumption by race/ethnicity among diverse samples (Marczinski, 2011), and to our knowledge, no studies have examined the direct correlation between caffeine withdrawal and race/ethnicity. Contrary to our results, demographic analyses from epidemiological studies show that for both children and adults, caffeine consumption is highest in the non-Hispanic white population and lowest in the non-Hispanic black population (Drewnowski & Rehm, 2016; Lieberman et al., 2016). However, a recent study found that caffeine-related problems were not associated with age, gender, or race/ethnicity among adolescents (Sojar, Shrier, Ziemnik, Sherritt, Spalding, & Levy, 2015).

Potential genetic liability towards caffeine metabolism or withdrawal could be a possible explanation for the present study's finding. However, this is an area that has received little attention due to concerns about subject population and/or population stratification (Yang, et al., 2010). Nonetheless, wide ethnic variations have been found for *CYP1A2* polymorphisms, and there appear to be variations in the association between *ADORA2A* and caffeine-induced anxiety in different ethnic groups (Lam et al. 2005; Yamada et al. 2001). Furthermore, the individual differences in response to caffeine at the metabolic (pharmacokinetic) or at the drug-receptor (pharmacodynamics) level, could contribute to the magnitude of caffeine withdrawal among this population. For example, Asian and African populations, appear to metabolize caffeine at slower rate than Caucasians (Gunes & Dahl, 2008). More studies in non-white ethnicities are needed to complete our understanding of genotype effects in responses to caffeine, however.

The present study also found that the probability of experiencing CWH significantly increased for participants who reported their biological mothers had problems with depression or anxiety. Unfortunately, due to the survey question and the correlational nature of our analysis, it is not possible to determine whether maternal problems with depression *or* anxiety are related to

CWH, but this finding extends research examining caffeine dependence and family histories. For example, Svikis and colleagues (2005) found in a sample of pregnant women, those with a lifetime diagnosis of caffeine dependence and a family history of alcoholism had higher levels of caffeine use, which as Svikis and colleagues postulated, suggests that a genetic susceptibility reflected in the family history of alcoholism may be essential to express the problematic features of caffeine dependence. Indeed, the results of the present study found that prevalence rates for CWH were highest among females and males reporting maternal alcohol use (27.7% and 25.6%, respectfully), and that significant relationships existed between CWH maternal and paternal alcohol use. However, multivariable analyses did not reveal these significant relationships in the final model. Nevertheless, the overall results of the present study do add to the literature which shows a greater co-occurrence of caffeine withdrawal in monozygotic than in dizygotic twin pairs, with heritabilities of these characteristics between 35% and 77% (Kendler & Prescott, 1999; Swan et al., 1996).

The present study also provides valuable new information about personality and caffeine withdrawal. Previous studies have described caffeine consumption being related to both general and specific personality traits; however, research on caffeine withdrawal and personality correlates has been limited (Jones & Lejuez, 2005). For example, Landrum (1992) demonstrated a positive correlation between caffeine consumption and Extroversion in a sample of college students, which could have been mediated by the specific constructs of Impulsivity and/or Sensation Seeking. In addition, Waldeck and Miller (1997) found that caffeine consumption was positively correlated with impulsivity in males, although not in females, and Jones & Lejuez (2005) found that caffeine consumption and dependence were positively correlated with Sensation Seeking and Impulsivity. Furthermore, a recent study conducted by Glen & Stephen

(2015) found a positive correlation between caffeine withdrawal and Impulsivity; however, the authors note that these results could be explained by other symptoms of stimulant withdrawal such as confusion or anxiety. It is hypothesized that because these personality constructs appear to share a temperamental low basal level of resting arousal (Pickering & Gray, 1999), people scoring high in these traits consume larger amount of caffeine to reach optimum level of activation.

The present study did not examine the relationship between CWH and Sensation Seeking or Impulsivity, however, results indicated that CWH was not significantly correlated with Extroversion. This is conflicting with the results found by Landrum (1992), though Landrum (1992) used the Caffeine Consumption Questionnaire which allowed for a precise and consistent measure of caffeine use but did not investigate symptoms of caffeine withdrawal, both of which could explain the differences in results.

Results of the present study did find that CWH was significantly associated with high scores in Neuroticism. Individuals who score high in neuroticism are typically people who tend to be anxious, high strung, tense and worrying, prone to depression, and cope poorly with stress (Friedman, 2011). This finding is of particular interest because additional results of the present study found significant associations between CWH and self-reported symptoms of depression and anxiety, corroborating results from a study examining caffeine use in teenagers (Bernstein, Carroll, Thuras, Cosgrove, and Roth, 2002) and in the general population (Broderick & Benjamin, 2004; Dosh, Helmbrecht, Anestis, Guenthner, Kelly, & Martin, 2010; James & Crosbie, 1987; Juliano et al., 2012). Furthermore, several personality factors, such as anxiety proneness, depression-proneness, impulsivity, and sensation seeking, have all been shown to be associated with risk for substance use patterns and disorders (Jones & Lejuez, 2005; Woicik et

al., 2009).

One possible explanation for this observation is that anxiety and Major Depressive Disorder have been found to share genetic and environmental factors with caffeine use and withdrawal (Bergin & Kendler, 2012; Kendler et al., 2006), which also substantiates our hypothesis to why we found CWH to be significantly associated with maternal depression or anxiety. Another explanation for our results could be due to the positive psychological and behavioral effects of caffeine. Desirable effects attributed to low or moderate intake levels, such as changes in mood, energy, alertness, and vigor, may mildly reinforce consumption for some individuals (Fredholm et al. 1999) and lead to withdrawal. Furthermore, some studies have identified a positive effect of caffeine on depression. For example, one study suggests that the chemical effects of caffeine can prevent brain receptors from responding to stressful situations, indicating that stressful responses don't manifest as easily in those with caffeine in their systems (Kaster, 2015). This response may also reinforce consumption for some and increase their risk for experiencing withdrawal.

Given that personality research has been helpful in identifying individual vulnerabilities to substance use and dependence (cf. Sher, Bartholow, & Wood, 2000), these results provide information that advances the caffeine withdrawal literature by identifying personality correlates that differentiate those people who experience the more negative symptoms of caffeine whereas others do not. Regardless of these results, it is imperative that research examining the constellation of correlated personality constructs with caffeine withdrawal continue so researchers and clinicians can generate relevant theoretical models for identifying the characteristics of caffeine dependence in clients and research participants.

Implications

The present study contributes new information to the existing literature on caffeine withdrawal. Specifically, while more than 66 experimental and survey studies have characterized various aspects of the caffeine withdrawal syndrome (Juliano & Griffith, 2004), and many contributed to caffeine withdrawal becoming recognized as a DSM-5 diagnosis (APA, 2013), few studies have focused on individual determinants and psychosocial correlates of caffeine withdrawal. The variables identified in the present study have the potential to inform development of targeted education and intervention efforts to prevent the development of caffeine-related problems.

Present study focus on college students is of particular importance as the use of energy drinks is quite common in this group, yet their knowledge of ingredients and potential health hazards of such drinks is often limited (Attila, 2011). Mixing energy drinks with alcohol is also common and has been associated with heavy drinking and adverse consequences.

Also, the finding that daily caffeine users are more likely to report CWH than non-daily users supports validity of self-report. This is important for both self-report data researchers and practitioners to know.

Study Limitations, Strengths and Future Directions

Limitations

First, our study relied solely on self-report measures of caffeine use frequency and CWH. While quantity of use is also important, measurement is more problematic because the variability in caffeine content and size across beverage types makes it difficult to standardize and assess accurately. Nonetheless, our findings offer some support for reliance upon frequency data, given

that daily users were in fact more likely to report CWH than non-daily users across beverage types.

A second limitation is that the data base did not contain information about daily caffeine use overall (i.e., "Do you consume something with caffeine in it every sing day?"). Instead, we looked separately at beverage type. We also looked at daily use of at least one caffeinated beverage typed. The present study also did not capture daily caffeine users who consumed different beverage types on different days (e.g., coffee 5 days per week and sodas on the two weekend days). Such daily users would be missed in the present study database and warrant further study.

Third, present study analyses focused on only one symptom of caffeine withdrawal (headaches). This was done because endorsement rates of the other symptoms were lower and headaches are the hallmark symptom of caffeine withdrawal. Future research should look at other symptoms as well.

Fourth, present study findings may be limited by the characteristics of the sample and should not be generalized without further study.

Fifth, this study did not examine all potentially important covariates of CWH. It is possible that other factors such as academic stress, physical activity, etc. may be important predictors of CWH. Also, other comorbid internalizing mood or substance use disorders were not measured and may be important.

A sixth limitation is use of univariable and multivariable analyses used for data analysis, which was unable to determine the direction of causality regarding 3-category variables. Additional statistical analyses such as Area Under the cure for the Receiver Operator

Characteristic curve, could have provided an "optimal" cut point for a score of the predictor variables, which simultaneously maximizes sensitivity and specificity.

Strengths

The current study has a number of strengths. First, it used a dataset collected from a large cohort of college freshmen. Second, whenever possible, standardized measures were used to assess study variables. When not available, existing measures were modified for the larger study. Third, the sample included nearly 70% of eligible participants. This is exceptional, given that when a meta-analysis (Cook, Health, & Thompson, 2000) looked at 68 US web-based surveys of college populations, they found a mean response rate of only 39.6%.

Fourth, the present study examined not only caffeine frequency of use measures, but also incidence of caffeine withdrawal symptoms. Fifth, since the Spit for Science project follows participants longitudinally over a four-year period (freshman to senior year), future research can examine longitudinal changes in caffeine use overtime. DNA data is also planned and can better contribute to our understanding of caffeine use, dependence, and withdrawal. In addition, new freshmen cohorts are now available and could be used to replicate present study findings.

Future Directions

Future research should seek to identify additional correlates of caffeine-related withdrawal symptoms, including whether genetic factors associated with caffeine metabolism further improves the ability to identify those at risk for caffeine withdrawal syndrome. For example, research findings have suggested that caffeine, as a component in coffee, may have adverse effects on cardiovascular health. In addition, linkage studies have shown that polymorphisms in the adenosine A2A receptor gene are associated with individual differences in caffeine consumption and caffeine's effects on EEG, anxiety, and sleep (Alsene et al., 2003;

Cornelis et al., 2007; Retey et al., 2007). These studies may help guide future research in the role of genetics in modulating the acute and chronic effects of caffeine. More work is likely needed to better understand the impact of genotypic differences in the human population and the subsequent interaction of lifestyle factors such as exposure to caffeine.

In addition, future research should determine whether caffeine serves as a gateway to other forms of drug dependence as suggested by some studies (Collins, El-Sohemy, & Campos, 1997; Pallanti, Bernardi, & Quercioli, 2006). With regard to energy drinks in particular, one study of 1,253 college students found that energy drink consumption significantly predicted subsequent nonmedical prescription stimulant use (Arria et al., 2010). It is plausible that the use of energy drinks that are promoted as alternatives to illicit drugs (e.g., "Cocaine") may, in fact, increase interest in the use of such drugs.

Also, and as previously discussed, individuals often underestimate their caffeine consumption because the caffeine content and other ingredients of caffeinated products are not always provided on nutritional labels. Future research should include a tool that yields a more accurate estimate of caffeine consumption (like the Caffeine Consumption Questionnaire or the Time-Line Follow Back survey) (Irons et al., 2016) that allows for researchers to invest more confidence in their data and resultant research findings, and for clinicians to gain a better understanding of consumption patterns that may be maladaptive. Furthermore, the evidence gathered from studies such as these could help inform government policy and educational programs to help the public become more aware of what they are consuming.

Conclusion

To our knowledge, this is the first study to examine individual and psychosocial factors associated with CWH in a large sample of college freshmen. Prevalence rates of caffeine use

were comparable to those in the literature. Further, a frequency measure, daily use of individuals of any caffeine source(s) was associated with CWH. Gender differences were found, with females being more likely to consume caffeine and experience CWH compared to males. In addition, the present study found that the probability of experiencing CWH significantly increased for females and non-white minority group members, and for those who were daily users of any caffeine product, reported peer problems with alcohol, scored high in neuroticism, and reported that their biological mother had problems with depression or anxiety. Future research will examine whether genetic factors also contribute to the experience of CWH. This study and others like will provide further valuable insights into the world's most widely consumed psychoactive substance.

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